Patent
Attorney's Docket No. 032013-103

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:	
Avraham COHEN et al.	Group Art Unit: 1625
Application No.: 10/507,485	Examiner: Margaret M. Seaman
Filed: September 13, 2004	Confirmation No.: 8571
For: ENANTIOMER (-) OF TENATOPROZOLE AND THE THERAPEUTIC USES THEREOF	

DECLARATION OF GEORGE SACHS PURSUANT 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, George Sachs, declare as follows:

1. I reside at 17986 Boris Drive Encino, CA 91316.

2. I am a citizen of the United States of America.

3. My educational background is as follows:

University of Edinburgh	1957	B.Sc., Biochemistry
University of Edinburgh	1960	M.B., Ch.B., Medicine
University of Edinburgh	1980	D.Sc. Biochemistry
University of Gothenburg	1987	M.D., Medicine

4. I am a Professor of Medicine and Physiology, Wilshire Chair in Medicine, and Director of Membrane Biology Lab at the University of California, Los Angeles and a Staff Physician at the Los Angeles VA Greater LA Healthcare System. I have been employed by the University of California, Los Angeles since 1982.

5. I have served on the Center for Ulcer Research and Education Executive Committee and Advisory Board since 1982 and I have been the director and co-director of the Center for Ulcer Research and Education.

6. I am a named author on more than three hundred (300) journal publications (peer-reviewed), more than sixty (60) published reviews, six (6) text books, seven (7) letters, and three (3) editorials.

7. My research interests are in the field of gastroenterology and the microbiology of *H. pylori*. Specifically, my research interests include membrane transport processes, pump mechanisms, epithelial cell function, and bacterial bioenergetics.

8. A copy of my complete Curriculum Vitae is attached as Exhibit A.

9. I am not an inventor of U.S. Patent Application Serial No. 10/507,485. However, I am familiar with the patent application, as well as the experimental data that has been generated with regard to the metabolism of tenatoprazole (namely, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]imidazo[4,5-b]pyridine), including the racemate, the R-enantiomer (the (+) enantiomer), and the S-enantiomer (the (-) enantiomer).

Background

10. Proton pump inhibitors (PPIs) are usually used for treating various acid-related diseases of the upper gastro-intestinal tract, especially gastro-oesophageal reflux disease (GERD). After accumulation at the level of the gastric parietal cell and after chemical rearrangement, proton pump inhibitors bind covalently to the enzyme responsible for the transport of protons into the gastric juice, and hence, irreversibly inhibit gastric acid secretion.

Tenatoprazole

11. Tenatoprazole is the result of research aimed at prolonging the plasma half-life (*i.e.*, residence time in the blood) of PPIs, through manipulations of the benzimidazole structure. Tenatoprazole is an imidazopyridine derivative, with an increased plasma half-life in humans.

12. The clinical development of the tenatoprazole racemic mixture has demonstrated the clinical significance of the long half-life. The inhibition of acid secretion caused by tenatoprazole was sustained throughout the night and thus, has resulted in earlier efficacy and relief in patients with GERD. Studies have provided evidence of non-proportionality between the augmentation of pharmacokinetic parameters and the increase in dose of racemic tenatoprazole. A high inter-subject variability of the pharmacokinetics and of the pharmacodynamic response (level of acid inhibition) has been seen. For example, one subject presented a six-fold increase in the exposure (*i.e.*, the area under the plasma concentrations/time curve (AUC)).

13. This observation triggered the implementation of a specific study to identify the human cytochromes involved in the metabolism of tenatoprazole racemate, the (+) enantiomer, and the (-) enantiomer.

In vitro Identification of Cytochromes involved in (+) and (-) Enantiomer Metabolism

14. An *in vitro* study of cytochromes involved in the metabolism of the (+) enantiomer and the (-) enantiomer of tenatoprazole (TU-199) was performed. I have reviewed the results of this study in detail. Data from the study is attached as Exhibit B.

15. The results of the *in vitro* metabolism study identified the human cytochromes involved in the metabolism of the (+) enantiomer and the (-) enantiomer of tenatoprazole, using cDNA-expressed human CYPs. It was determined that CYP 2C19 is involved in 80 % of the metabolism of (+) enantiomer of tenatoprazole. For the (-) enantiomer, it was determined that CYP 2C19 was involved in only 53.4 % of the metabolism, and importantly, it was identified that CYP 3A4 was involved in 27.3 % of the metabolism and CYP 2C9 was involved in 19.3 % of the metabolism of this enantiomer.

16. Accordingly, CYP 2C19 is the dominant pathway for the metabolism of the (+) enantiomer of tenatoprazole. In contrast, pathways other than CYP 2C19 exist for metabolism of the (-) enantiomer (*i.e.*, CYP 3A4 and CYP 2C9).

17. Subjects with a genetic deficiency of the CYP 2C19 pathway (so called "poor metabolizers") account for the observed high inter-subject variability of the pharmacokinetics and of the pharmacodynamic response (level of acid inhibition) when dosing with the tenatoprazole racemate and the (+) enantiomer. These "poor metabolizers" have increased half-life and exposure (*i.e.*, the area under the plasma concentrations/time curve (AUC)), raising potential safety concerns.

18. In contrast, the (-) enantiomer has "escape" metabolic pathways in subjects with a genetic deficiency of the CYP 2C19 pathway (*i.e.*, CYP 3A4 and CYP 2C9). Therefore, even these "poor metabolizer" subjects can metabolize the (-) enantiomer. As such, the (-) enantiomer

exhibits a predictable half-life and exposure even in these "poor metabolizers" and therefore, can be dosed more safely and predictably in all subjects.

19. The incidence of so-called "poor metabolizers" is about 3 % in Caucasians and over 20 % in Asians and 6% in Hispanics.

Study of single and repeated oral administration of tenatoprazole racemate and enantiomers

20. A double blind, placebo controlled study on the tolerability of single and repeated dosing of tenatoprazole racemate (TU-199), as well as the (+) and (-) enantiomers, in healthy males was performed. I have reviewed the results of this study in detail. Data from the study is attached as Exhibit B.

21. In this study, the tenatoprazole racemate (TU-199), as well as the (+) and (-) enantiomers of tenatoprazole, were administered to sets of eight subjects per dose. The drug was administered once per day on day 1 of the study (the single administration phase) and then administration was resumed at once per day on days 14-20 (the repeated administration phase). C_{max} (maximum concentrations), T_{max} (maxiumum time), AUC (area under the curve) and $t_{1/2}$ (half-life) were determined for the racemate, as well as the (+) and (-) enantiomer. Values for "poor metabolizers" were not included in this data.

22. In the data in attached Exhibit B, it is seen that the pharmacokinetics of the racemate are not linear, and it is seen that the pharmacokinetics of the (+) enantiomer also are not linear. However, it is surprisingly seen that the pharmacokinetics of the (-) enantiomer are linear. Since the pharmacokinetics of the (-) enantiomer are linear, the non-linearity of the tenatoprazole racemate is due specifically to the (+) enantiomer.

23. The non-linear profile of the (+) enantiomer and the racemate result in unpredictability and reduction in safety in dosing in all patients since there is no proportionality between the increase in dose and increase in plasma concentrations. In contrast, the (-) enantiomer exhibits a linear profile providing predictability in dosing in all patients and increased safety since there is proportionality between the increase in dose and increase in plasma concentrations.

24. The metabolic by-products of the (+) enantiomer exhibit an inhibitory effect on the metabolism of the (+) enantiomer. This data further shows that the (+) enantiomer, and the racemate, are unpredictable in patient dosing.

Study of pharmacokinetics of tenatoprazole racemate and enantiomers in extensive and poor metabolizers

25. An open-label parallel-group study on the pharmacokinetics of the tenatoprazole racemate (TU-199), the (+) enantiomer, and the (-) enantiomer after single oral dose administration in extensive and poor CYP2C19 metabolizers was performed. I have reviewed the results of this study in detail. Data from the study is attached as Exhibit B. The "extensive metabolizers" do not have the genetic deficiency of the CYP 2C19 pathway and are considered "normal" subjects.

26. In this study, the tenatoprazole racemate (TU-199), as well as the (+) and (-) enantiomers of tenatoprazole, were administered to eight healthy volunteers (four poor metabolizers and four extensive metabolizers). The volunteers were given a single 20 mg oral dose under fasting conditions. The study period was 192 hours after administration for the poor metabolizers and 72 hours after administration for the extensive metabolizers. The C_{max}, T_{max}, AUC and $t_{1/2}$ of TU-199 (+) enantiomer, and (-) enantiomer were determined.

27. When comparing the C_{max}, T_{max}, AUC and $t_{1/2}$ for the racemate and the (+) enantiomer for the poor metabolizers and the extensive metabolizers, drastic differences are observed. However,

for the poor metabolizers and the extensive metabolizers, unexpectedly, there is no significant pharmacokinetic variation in the C_{max}, T_{max}, AUC and $t_{1/2}$ for the (-) enantiomer.

28. The mean exposure (AUC) to tenatoprazole racemate (TU-199) was found to be over four-fold higher in poor metabolizers in comparison to extensive metabolizers. The elimination half-life ($t_{1/2}$) of the tenatoprazole racemate (TU-199) was about 30 hours in poor metabolizers, compared to 6 hours in extensive metabolizers.

29. Unexpectedly, this difference is due to the (+) enantiomer. The mean exposure (AUC) to the (+) enantiomer was found to be over 21-fold higher in the same poor metabolizers in comparison to the same extensive metabolizers (*i.e.*, 173,996 ng/h/mL^{-1} vs. 8,085 ng/h/mL^{-1}). In addition, the half-life ($t_{1/2}$) was increased by eight-fold (36.7 vs. 4.5 hours).

30. In contrast, the (-) enantiomer showed only a slightly increased half-life in the same poor metabolizers in comparison to the same extensive metabolizers (*i.e.*, 9.7 vs. 5.7 hours).

Conclusions

31. Unexpectedly, the pharmacokinetics of (-) enantiomer are linear in both subjects without a genetic deficiency of the CYP 2C19 pathway ("normal subjects") and in subjects with a genetic deficiency of the CYP 2C19 pathway ("poor metabolizers"). The linearity allows for predictability in dosing in all patients, thus providing increased safety in dosing in all patients.

32. Also unexpectedly, the pharmacokinetics of (+) enantiomer are not linear in either subjects without a genetic deficiency of the CYP 2C19 pathway ("normal subjects") or in subjects with a genetic deficiency of the CYP 2C19 pathway ("poor metabolizers"). The metabolic by-products of the (+) enantiomer exhibit an inhibitory effect on the metabolism of the (+) enantiomer. Possible safety concerns arise from the poor predictability in dosing in all

patients, the increased half life and exposure in patients, and the increased potential for drug interactions.

33. In summary, the (-) enantiomer has a predictable pharmacodynamic response, due to its linear pharmacokinetic response to dosing. The racemate and the (+) enantiomer are not predictable in this way. The (-) enantiomer showed a lower variability in metabolism in both subjects without a genetic deficiency of the CYP 2C19 pathway ("normal subjects") or in subjects with a genetic deficiency of the CYP 2C19 pathway ("poor metabolizers"). Therefore, the (-) enantiomer could be administered to any subject, without considering the subject's CYP 2C19 polymorphism status.

34. Moreover, it is my opinion that it is unexpected that the (-) enantiomer of tenatoprazole exhibits such a different pharmacokinetic profile, in comparison to the tenatoprazole racemate and the (+) enantiomer.

I further declare that all statements made herein of my own knowledge are true and that all statements on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 10/26/05

George Sachs

CURRICULUM VITAE

PERSONAL HISTORY:

NAME: George Sachs

WORK ADDRESS: Membrane Biology Laboratory, VAGLAHS-West Los Angeles, 11301 Wilshire Blvd., Bldg. 113, Rm. 324, Los Angeles, C.A., 90073
(310)268-3923

HOME ADDRESS: 17986 Boris Drive
Encino, CA. 91316
(818)344-3484

BIRTHDATE: August 26, 1935

PLACE OF BIRTH: Vienna, Austria

CITIZENSHIP: U.S.A.

EDUCATION:

University of Edinburgh	1957	B.Sc., first class honors	Biochemistry
University of Edinburgh	1960	M.B., Ch.B., with honors	Medicine
University of Edinburgh	1980	D.Sc.	Biochemistry
University of Gothenburg	1987	M.D., (Hon Causa)	Medicine

LICENSURE: California, Physician and Surgeon #A 54208

PROFESSIONAL EXPERIENCE:

PRESENT POSITIONS:

University of California, Los Angeles	1982-present	Professor, Medicine & Physiology
University of California, Los Angeles	1982-present	Wilshire Chair in Medicine
University of California, Los Angeles	1987-present	Director, Membrane Biology Laboratory
VAGLAHS-West Los Angeles	1999-present	Staff Physician

PREVIOUS POSITIONS:

Albert Einstein College	1961-1962	Instructor
Columbia University	1962-1963	Research Associate

University of Alabama in Birmingham	1963-1965	Assistant Professor, Medicine & Physiology
University of Alabama in Birmingham	1965-1970	Associate Professor, Medicine & Physiology
University of Alabama in Birmingham	1970-1982	Prof. Medicine & Physiology
University of Alabama in Birmingham	1974-1982	Director, Membrane Biology
University of Alabama in Birmingham	1979-1982	Professor, Medicine & Physiology & Biophysics
University of California, Los Angeles	1982-1987	Director, Center for Ulcer Research & Education
VAGLAHS-West Los Angeles	1984-1999	Senior Medical Investigator
University of California, Los Angeles	1987-2003	Co-Director, Center for Ulcer Research & Education

PROFESSIONAL ACTIVITIES:

COMMITTEE SERVICES:

National:
National Committee Biophysical Society, 1976-1978
NSF Panel for Metabolic Biology, 1977-1979
American Physiological Society GI Steering Committee, 1977-1981
NIH Study Section, Physiology, 1979-1983
National Board Medical Examiners, 1979-1983
VA Merit Review Board, 1984-1987
National Committee Biophysical Society, 1987-1989
NIAMS, Board of Scientific Counselors, NIH, 1993
NIH Study Section NIDDK Digestive Disease Centers, 2000-Present
NIH Advisory Board, 2002
NIH Study Section NIDDK Digestive Disease Centers, 2002-Present
NIH Special Study Section, 2003-Present

Local:
Center for Ulcer Research and Education Executive Committee, 1982-Present
Center for Ulcer Research and Education Advisory Board, 1982-Present
Veterans Administration Review Committee, 1983-1986
IBD/Harbor UCLA Advisory Board, 1988-1992
Chair, Academic Personnel Committee, UCLA, 1990-1991
GI/UCLA Search Committee, 1992-1993
UCLA Specialty Training and Academic Research Committee (STAR), 1993-1995
UCLA, Academic Personnel ad hoc Review Committee, 1994
VAMC, Wadsworth, ACOS for Research Search Committee, 1994
VAMC, West Los Angeles R&D, GI and Hepatic Disorder Review Group, 1996
VAMC, West Los Angeles Merit Review Committee, 1996
VAMC, West Los Angeles Internal Merit Review Committee, 1996
VAGLAHS-West Los Angeles, Chair, Research Sub-Committee, 2000-Present

PROFESSIONAL ASSOCIATIONS:

American Gastroenterological Association
American Physiological Society

American Society for Biochemistry and Molecular Biology
American Society of Biological Chemistry
American Society for Microbiology
American Society of Renal Biochemistry and Metabolism
Biochemical Society
British Gastroenterological Association (Honorary)
Society of General Physiology

EDITORIAL SERVICES:

American Journal of Physiology, Editorial Board, 1968-1977
American Journal of Physiology, Associate Editor, 1977-1985
Hypertension, Editorial Board, 1982-1985
Physiological Reviews, Editorial Board, 1983-1989
Annual Review of Physiology, Associate Editor, 1985-1990
American Journal of Physiology, Editorial Board, 1985-Present
American Heart Association, Review Board, 1988-1991
Alimentary Pharmacology & Therapeutics, Editorial Board, 1988-2004
Digestive Diseases and Sciences, Editorial Board, 1990-Present
Frontiers of Bioscience, Editorial Board, 2001
World Journal of Gastroenterology, Editorial Board, 2004-Present
Reviewer, Biochemistry, 2004-Present

HONORS AND SPECIAL AWARDS RECEIVED:

Humboldt Award for U.S. Senior Scientists, 1973-1974
Hoffman LaRoche Award, 1982
Senior Medical Investigatorship, Veterans Administration, 1984-1999
Beaumont Prize in Gastroenterology, American Gastroenterological Association, 1985
Middleton Award, Veterans Administration, 1992
"Ismar Boas Vorlesung" Medal, German Gastroenterological Association, 1992
Fifth "Morton I. Grossman Distinguished Lectureship", 1993
Honorary Membership, British Society of Gastroenterology, 1993
Distinguished Lecturer, Department of Pharmacology, University Texas Medical School at Houston, 1995
Outstanding Scientific and Technical Award, Federal Executive Board of Los Angeles, 1996
Honorary Degree, Doctor of Medicine, Medical Faculty of Gothenburg University, Sweden, 1996
Horace W. Davenport Distinguished Lecturer of the APS Gastrointestinal Section, 1998
Janssen Award for Special Achievement in Gastroenterology, 1998
Outstanding Scientific and Technical Award, Federal Executive Board of Los Angeles, 1998
Outstanding Supporter, Upward Bound Internship Program Harvey Mudd College, 2000
Gairdner Foundation Awardee, 2004
Dr. Norman Frankel Scholar to the University of Chicago, 2005

BIBLIOGRAPHY

Journal Publications (Peer-Reviewed):

1. G. Sachs and O. Braun-Falco. The occurrence and nature of arylsulfatases in parakeratoses. *J.Invest Dermatol.* 34:439-444, 1960.
2. G. Sachs, C. Deduve, B. S. Dvorkin, and A. White. Effect of adrenal cortical steroid injection on lysosmal enzymic activities of rat thymus. *Exp.Cell Res.* 28:597-600, 1962.
3. G. C. Luketic, J. Myren, G. Sachs, and B. I. Hirschowitz. Effect of therapeutic doses of colchicines on oxidative enzymes in the intestine. *Nature* 202:608-609, 1964.
4. W. W. Duke, B. I. Hirschowitz, and G. Sachs. Vagal stimulation of gastric secretion in man by 2-deoxy-D-glucose. *Lancet* 2 (7418):871-876, 1965.
5. B. I. Hirschowitz and G. Sachs. Vagal gastric secretory stimulation by 2-deoxy-D-glucose. *Am.J.Physiol* 209 (3):452-460, 1965.
6. G. Sachs and B. I. Hirschowitz. Effect of diisopropyl fluorophosphate on gastric secretion and gastric ATPase. *Proc.Soc.Exp.Biol.Med.* 120 (3):702-704, 1965.
7. G. Sachs, R. Shoemaker, and B. I. Hirschowitz. Action of 2-deoxy-D-glucose on frog gastric mucosa. *Am.J.Physiol* 209 (3):461-466, 1965.
8. G. Sachs, W. E. Mitch, and B. I. Hirschowitz. Frog gastric mucosal ATPase. *Proc.Soc.Exp.Biol.Med.* 119 (4):1023-1027, 1965.
9. B. I. Hirschowitz and G. Sachs. Reversal of insulin inhibition of gastric secretion by intravenous injection of potassium. *Am.J.Dig.Dis.* 11 (3):217-230, 1966.
10. G. C. Luketic, G. Sachs, J. Myren, T. Tsuji, and B. I. Hirschowitz. Effects of colchicine on intestinal mucosal dehydrogenases. II. Biochemical observations. *Am.J.Dig.Dis.* 11 (5):404-409, 1966.
11. J. Myren, G. C. Luketic, R. Ceballos, G. Sachs, and B. I. Hirschowitz. Effects of colchicine on intestinal mucosal dehydrogenases. I. Histochemical observations. *Am.J.Dig.Dis.* 11 (5):394-403, 1966.
12. G. Sachs, R. L. Shoemaker, and B. L. Hirschowitz. Effects of sodium removal on acid secretion by the frog gastric mucosa. *Proc.Soc.Exp.Biol.Med.* 123 (1):47-52, 1966.
13. R. L. Shoemaker, G. Sachs, and B. I. Hirschowitz. Secretion by guinea pig gastric mucosa in vitro. *Proc.Soc.Exp.Biol.Med.* 123 (3):824-827, 1966.
14. B. I. Hirschowitz and G. Sachs. Insulin inhibition of gastric secretion: reversal by ribidium. *Am.J.Physiol* 213 (6):1401-1405, 1967.
15. B. I. Hirschowitz and G. Sachs. Insulin effects on gastric secretion and blood electrolytes modified by injected potassium. *Am.J.Dig.Dis.* 12 (1):7-18, 1967.
16. A. G. Ramsay and G. Sachs. Effect of ouabain on Na+ and K+ excretion in the rat. *Proc.Soc.Exp.Biol.Med.* 126 (1):294-298, 1967.
17. G. Sachs, J. D. Rose, and B. I. Hirschowitz. Acetyl phosphatase in brain microsomes: a partial reaction of Na+ plus K+ ATPase. *Arch.Biochem.Biophys.* 119 (1):277-281, 1967.
18. G. Sachs, R. Shoemaker, and B. I. Hirschowitz. The action of amytal on frog gastric mucosa. *Biochim.Biophys.Acta* 143 (3):522-531, 1967.
19. R. L. Shoemaker, B. I. Hirschowitz, and G. Sachs. Hormonal stimulation of Necturus gastric mucosa in vitro. *Am.J.Physiol* 212 (5):1013-1016, 1967.
20. L. C. Clark, Jr. and G. Sachs. Bioelectrodes for tissue metabolism. *Ann.N.Y.Acad.Sci.* 148 (1):133-153, 1968.
21. B. I. Hirschowitz and G. Sachs. Restoration of homeostasis during histamine-stimulated gastric secretion by rapid intravenous injection of KCl. *Gastroenterology* 54 (5):898-906, 1968.
22. G. Sachs, R. H. Collier, R. L. Shoemaker, and B. I. Hirschowitz. The energy source for gastric H+ secretion. *Biochim.Biophys.Acta* 162 (2):210-219, 1968.
23. T. Tsuji, B. I. Hirschowitz, and G. Sachs. Murine hepatitis virus: effect on liver RNA. *Science* 159 (818):987-990, 1968.

24. B. I. Hirschowitz and G. Sachs. Atropine inhibition of insulin-, histamine-, and pentagastrin-stimulated gastric electrolyte and pepsin secretion in the dog. *Gastroenterology* 56 (4):693-702, 1969.
25. B. I. Hirschowitz and G. Sachs. Pentagastrin in the gastric fistula dog. *Gastroenterology* 56 (3):456-467, 1969.
26. G. Sachs, E. Z. Finley, T. Tsuji, and B. I. Hirschowitz. Effect of irreversible inhibitors on transport ATPase. *Arch.Biochem.Biophys.* 134 (2):497-499, 1969.
27. G. Sachs, R. H. Collier, A. Pacifico, R. L. Shoemaker, R. A. Zweig, and B. I. Hirschowitz. Action of thiocyanate on gastric mucosa in vitro. *Biochim.Biophys.Acta* 173 (3):509-517, 1969.
28. M. Cochran, M. Peacock, G. Sachs, and B. E. Nordin. Renal effects of calcitonin. *Br.Med.J.* 1 (689):135-137, 1970.
29. S. Nakajima, R. L. Shoemaker, B. I. Hirschowitz, and G. Sachs. Comparison of actions of aminophylline and pentagastrin on Necturus gastric mucosa. *Am.J.Physiol* 219 (5):1259-1262, 1970.
30. S. Nakajima, R. L. Shoemaker, B. I. Hirschowitz, and G. Sachs. Influence of atropine on resistance, potential, and H+ secretion in isolated gastric mucosa. *Am.J.Physiol* 218 (4):990-994, 1970.
31. G. Sachs, L. C. Clark, and G. M. Makhlouf. The use of fluorocarbon emulsion in the Ussing chamber. *Proc.Soc.Exp.Biol.Med.* 134 (3):694-695, 1970.
32. G. Sachs, R. H. Collier, and B. I. Hirschowitz. Action of SCN- on rat liver mitochondria. *Proc.Soc.Exp.Biol.Med.* 133 (2):456-459, 1970.
33. R. L. Shoemaker, G. M. Makhlouf, and G. Sachs. Action of cholinergic drugs on Necturus gastric mucosa. *Am.J.Physiol* 219 (4):1056-1060, 1970.
34. H. L. Spitzer, G. Sachs, and L. C. Clark, Jr. Fluorocarbon effects on tissue metabolism. *Fed.Proc.* 29 (5):1746-1750, 1970.
35. N. Avdalovic and G. Sachs. (Na plus minus K+)-APTase in the kidney of normal and castrated mice. *Biochim.Biophys.Acta* 237 (1):137-140, 1971.
36. A. L. Blum, G. Shah, Pierre T. St, H. F. Helander, C. P. Sung, V. D. Wiebelhaus, and G. Sachs. Properties of soluble ATPase of gastric mucosa. I. Effect of HCO 3 -. *Biochim.Biophys.Acta* 249 (1):101-113, 1971.
37. A. L. Blum, B. I. Hirschowitz, H. F. Helander, and G. Sachs. Electrical properties of isolated cells of Necturus gastric mucosa. *Biochim.Biophys.Acta* 241 (2):261-272, 1971.
38. A. L. Blum, G. T. Shah, V. D. Wiebelhaus, F. T. Brennan, H. F. Helander, R. Ceballos, and G. Sachs. Pronase method for isolation of viable cells from Necturus gastric mucosa. *Gastroenterology* 61 (2):189-200, 1971.
39. S. Nakajima, B. I. Hirschowitz, R. L. Shoemaker, and G. Sachs. Inhibition of gastric acid secretion in vitro by C-terminal octapeptide of cholecystokinin. *Am.J.Physiol* 221 (4):1009-1013, 1971.
40. S. Nakajima, B. I. Hirschowitz, and G. Sachs. Studies on adenyl cyclase in Necturus gastric mucosa. *Arch.Biochem.Biophys.* 143 (1):123-126, 1971.
41. G. Sachs, M. M. Long, T. Tsuji, and B. I. Hirschowitz. The effect of hydroxylamine on transport ATPase. *Biochim.Biophys.Acta* 233 (1):117-121, 1971.
42. I. A. Sirakova, L. M. Sirakov, G. Sachs, and G. C. Luketic. Effect of colchicine on the synthesis of ribonucleic acid in mouse intestinal mucosa. *Biochem.Pharmacol.* 20 (8):1943-1949, 1971.
43. V. D. Wiebelhaus, C. P. Sung, H. F. Helander, G. Shah, A. L. Blum, and G. Sachs. Solubilization of anion ATPase from necturus oxyntic cells. *Biochim.Biophys.Acta* 241 (1):49-56, 1971.
44. M. C. Goodall and G. Sachs. Extraction of K + selective channels from excitable tissue. *Nat.New Biol.* 237 (77):252-253, 1972.
45. B. I. Hirschowitz and G. Sachs. KCl reversal of insulin inhibition and fade in pentagastrin-stimulated gastric secretion. *Am.J.Physiol* 223 (2):305-309, 1972.
46. B. I. Hirschowitz, G. Hutchison, and G. Sachs. Kinetics of atropine inhibition of histamine-stimulated gastric secretion in the dog. *Am.J.Physiol* 222 (5):1316-1321, 1972.

47. C. A. Kessler, B. I. Hirschowitz, P. G. Burhol, and G. Sachs. Methoxyflurane (Penthrane) anesthesia effect on histamine simulated gastric secretion in the chicken. *Proc.Soc.Exp.Biol.Med.* 139 (4):1340-1343, 1972.
48. L. Masotti, M. M. Long, G. Sachs, and D. W. Urry. The effects of ATP on the CD spectrum of membrane fraction from oxyntic cells. *Biochim.Biophys.Acta* 255 (1):420-424, 1972.
49. G. Sachs, G. Shah, A. Strych, G. Cline, and B. I. Hirschowitz. Properties of ATPase of gastric mucosa. 3. Distribution of HCO 3 -stimulated ATPase in gastric mucosa. *Biochim.Biophys.Acta* 266 (3):625-638, 1972.
50. B. Simon, R. Kinne, and G. Sachs. The presence of a HCO 3 - -ATPase in pancreatic tissue. *Biochim.Biophys.Acta* 282 (1):293-300, 1972.
51. C. P. Sung, V. D. Wiebelhaus, B. C. Jenkins, P. Adlercreutz, B. I. Hirschowitz, and G. Sachs. Heterogeneity of 3',5'-phosphodiesterase of gastric mucosa. *Am.J.Physiol* 223 (3):648-650, 1972.
52. B. I. Hirschowitz, G. Sachs, and G. Hutchison. Lack of potentiation or synergism between histamine and pentagastrin in the fistula dog. *Am.J.Physiol* 224 (3):509-513, 1973.
53. B. I. Hirschowitz, G. A. Hutchison, and G. Sachs. Kinetics of atropine and Diamox inhibition of histamine-stimulated gastric secretion. *Scand.J.Gastroenterol.* 8 (6):555-559, 1973.
54. M. M. Long, L. Masotti, G. Sachs, and D. W. Urry. Circular dichroism of biological membranes-brain microsomes. *J.Supramol.Struct.* 1 (4):259-268, 1973.
55. G. Sachs, J. G. Spenney, R. L. Shoemaker, and M. C. Goodall. Conductance pathways in epithelial tissues. *Exp.Eye Res.* 16 (4):241-249, 1973.
56. J. G. Spenney, A. Strych, A. H. Price, H. F. Helander, and G. Sachs. Properties of ATPase of gastric mucosa. V. Preparation of membranes and mitochondria by zonal centrifugation. *Biochim.Biophys.Acta* 311 (4):545-564, 1973.
57. C. P. Sung, B. C. Jenkins, L. R. Burns, V. Hackney, J. G. Spenney, G. Sachs, and V. D. Wiebelhaus. Adenyl and guanyl cyclase in rabbit gastric mucosa. *Am.J.Physiol* 225 (6):1359-1363, 1973.
58. G. Saccomani, J. G. Spenney, D. W. Urry, and G. Sachs. Preparation and characterization of plasma membrane of cardiac tissue. *J.Mol.Cell Cardiol.* 6 (6):505-521, 1974.
59. R. L. Shoemaker, E. Buckner, J. G. Spenney, and G. Sachs. Action of Burimamide, a histamine antagonist, on acid secretion in vitro. *Am.J.Physiol* 226 (4):898-902, 1974.
60. J. G. Spenney, G. Saccomani, H. L. Spitzer, M. Tomana, and G. Sachs. Characterization of gastric mucosal membranes. Composition of gastric cell membranes and polypeptide fractionation using ionic and nonionic detergents. *Arch.Biochem.Biophys.* 161 (2):456-471, 1974.
61. J. G. Spenney, R. L. Shoemaker, and G. Sachs. Microelectrode studies of fundic gastric mucosa: cellular coupling and shunt conductance. *J.Membr.Biol.* 19 (1):105-128, 1974.
62. V. D. Wiebelhaus, A. L. Blum, and G. Sachs. Isolation of oxyntic cells. *Methods Enzymol.* 32 (Part B):707-717, 1974.
63. R. Kinne, H. Murer, E. Kinne-Saffran, M. Thees, and G. Sachs. Sugar transport by renal plasma membrane vesicles. Characterization of the systems in the brush-border microvilli and basal-lateral plasma membranes. *J.Membr.Biol.* 21 (3-4):375-395, 1975.
64. R. Kinne, H. Murer, E. Kinne-Saffran, M. Thees, and G. Sachs. Sugar transport by renal plasma membrane vesicles Characterization of the systems in the brush-border microvilli and basal-lateral plasma membranes. *J.Membr.Biol.* 21 (3-4):375-955, 1975.
65. G. Saccomani, G. Shah, J. G. Spenney, and G. Sachs. Characterization of gastric mucosal membranes. VIII.The localization of peptides by iodination and phosphorylation. *J.Biol.Chem.* 250 (12):4802-4809, 1975.
66. G. Sachs, E. Rabon, G. Saccomani, and H. M. Sarau. Redox and ATP in acid secretion. *Ann.N.Y.Acad.Sci.* 264:456-475, 1975.
67. J. G. Spenney, G. Flemstrom, R. L. Shoemaker, and G. Sachs. Quantitation of conductance pathways in antral gastric mucosa. *J.Gen.Physiol* 65 (5):645-662, 1975.

68. A. G. Ramsay, D. L. Gallagher, R. L. Shoemaker, and G. Sachs. Barium inhibition of sodium ion transport in toad bladder. *Biochim.Biophys.Acta* 436 (3):617-627, 1976.
69. G. Sachs, H. H. Chang, E. Rabon, R. Schackman, M. Lewin, and G. Saccomani. A nonelectrogenic H+ pump in plasma membranes of hog stomach. *J.Biol.Chem.* 251 (23):7690-7698, 1976.
70. S. C. Bajaj, J. G. Spenney, and G. Sachs. Properties of gastric antrum. III. Selectivity and modification of shunt conductance. *Gastroenterology* 72 (1):72-77, 1977.
71. H. Chang, G. Saccomani, E. Rabon, R. Schackmann, and G. Sachs. Proton transport by gastric membrane vesicles. *Biochim.Biophys.Acta* 464 (2):313-327, 1977.
72. M. C. Goodall and G. Sachs. Reconstitution of a proton pump from gastric mucosa. *J.Membr.Biol.* 35 (4):285-301, 1977.
73. R. J. Jackson, H. B. Stewart, and G. Sachs. Isolation and purification of normal and malignant colonic plasma membranes. *Cancer* 40 (5 Suppl):2487-2496, 1977.
74. J. I. Kreisberg, G. Sachs, T. G. Pretlow, and R. A. McGuire. Separation of proximal tubule cells from suspensions of rat kidney cells by free-flow electrophoresis. *J.Cell Physiol* 93 (1):169-172, 1977.
75. M. Lewin, G. Saccomani, R. Schackmann, and G. Sachs. Use of 1-anilino-8-naphthalene-sulfonate as a probe of gastric vesicle transport. *J.Membr.Biol.* 32 (3-4):301-318, 1977.
76. S. Milutinovic, B. E. Argent, U. Schulz, and G. Sachs. Studies on isolated subcellular components of cat pancreas. II. A Ca++-dependent interaction between membranes and zymogen granules of cat pancreas. *J.Membr.Biol.* 36 (2-3):281-295, 1977.
77. S. Milutinovic, G. Sachs, W. Haase, and I. Schulz. Studies on isolated subcellular components of cat pancreas. I. Isolation and enzymatic characterization. *J.Membr.Biol.* 36 (2-3):253-279, 1977.
78. E. C. Rabon, H. M. Sarau, W. S. Rehm, and G. Sachs. Redox involvement in acid secretion in the amphibian gastric mucosa. *J.Membr.Biol.* 35 (3):189-204, 1977.
79. G. Sachs. Ion pumps in the renal tubule. *Am.J.Physiol* 233 (5):F359-F365, 1977.
80. G. Sachs, H. Chang, E. Rabon, R. Shackman, H. M. Sarau, and G. Saccomani. Metabolic and membrane aspects of gastric H+ transport. *Gastroenterology* 73 (4 Pt 2):931-940, 1977.
81. H. M. Sarau, J. J. Foley, G. Moonsammy, and G. Sachs. Metabolism of dog gastric mucosa. Levels of glycolytic, citric acid cycle and other intermediates. *J.Biol.Chem.* 252 (23):8572-8581, 1977.
82. R. Schackmann, A. Schwartz, G. Saccomani, and G. Sachs. Cation transport by gastric H+:K+ ATPase. *J.Membr.Biol.* 32 (3-4):361-381, 1977.
83. R. Iyengar, D. S. Mailman, and G. Sachs. Purification of distinct plasma membranes from canine renal medulla. *Am.J.Physiol* 234 (3):F247-F254, 1978.
84. H. R. Koelz, J. A. Fischer, G. Sachs, and A. L. Blum. Specific effect of acetylsalicylic acid on cation transport of isolated gastric mucosal cells. *Am.J.Physiol* 235 (1):E16-E21, 1978.
85. E. Rabon, H. Chang, and G. Sachs. Quantitation of hydrogen ion and potential gradients in gastric plasma membrane vesicles. *Biochemistry* 17 (16):3345-3353, 1978.
86. T. Berglindh, H. Helander, and G. Sachs. Secretion at the parietal cell level--a look at rabbit gastric glands. *Scand.J.Gastroenterol.Suppl* 55:7-20, 1979.
87. D. R. Dibona, S. Ito, T. Berglindh, and G. Sachs. Cellular site of gastric acid secretion. *Proc.Natl.Acad.Sci.U.S.A* 76 (12):6689-6693, 1979.
88. A. K. Mircheff, G. Sachs, S. D. Hanna, C. S. Labiner, E. Rabon, A. P. Douglas, M. W. Walling, and E. M. Wright. Highly purified basal lateral plasma membranes from rat duodenum. Physical criteria for purity. *J.Membr.Biol.* 50 (3-4):343-363, 1979.
89. E. Rabon, I. Kajdos, and G. Sachs. Induction of a chloride conductance in gastric vesicles by limited trypsin or chymotrypsin digestion or ageing. *Biochim.Biophys.Acta* 556 (3):469-478, 1979.
90. E. Rabon, G. Saccomani, D. K. Kasbekar, and G. Sachs. Transport characteristics of frog gastric membranes. *Biochim.Biophys.Acta* 551 (2):432-447, 1979.

91. G. Saccomani, H. F. Helander, S. Crago, H. H. Chang, D. W. Dailey, and G. Sachs. Characterization of gastric mucosal membranes. X. Immunological studies of gastric (H+ + K+)-ATPase. *J.Cell Biol.* 83 (2 Pt 1):271-283, 1979.
92. G. Saccomani, H. H. Chang, A. A. Mihas, S. Crago, and G. Sachs. An acid transporting enzyme in human gastric mucosa. *J.Clin.Invest* 64 (2):627-635, 1979.
93. G. Saccomani, D. W. Dailey, and G. Sachs. The action of trypsin on the gastric (H+ + K+)-ATPase. *J.Biol.Chem.* 254 (8):2821-2827, 1979.
94. G. Saccomani, H. H. Chang, A. Spisni, H. F. Helander, H. L. Spitzer, and G. Sachs. Effect of phospholipase A2 on purified gastric vesicles. *J.Supramol.Struct.* 11 (4):429-444, 1979.
95. T. Berglindh, G. Sachs, and N. Takeguchi. Ca2+-dependent secretagogue stimulation in isolated rabbit gastric glands. *Am.J.Physiol* 239 (2):G90-G94, 1980.
96. T. Berglindh, D. R. Dibona, C. S. Pace, and G. Sachs. ATP dependence of H+ secretion. *J.Cell Biol.* 85 (2):392-401, 1980.
97. T. Berglindh, D. R. Dibona, S. Ito, and G. Sachs. Probes of parietal cell function. *Am.J.Physiol* 238 (3):G165-G176, 1980.
98. C. S. Chew, S. J. Hersey, G. Sachs, and T. Berglindh. Histamine responsiveness of isolated gastric glands. *Am.J.Physiol* 238 (4):G312-G320, 1980.
99. C. N. Graves, G. Sachs, and W. S. Rehm. Use of a fluorescent cyanine dye for electrophysiological studies on the frog cornea. *Am.J.Physiol* 238 (1):C21-C26, 1980.
100. E. Rabon, N. Takeguchi, and G. Sachs. Water and salt permeability of gastric vesicles. *J.Membr.Biol.* 53 (2):109-117, 1980.
101. G. Sachs. Vanadate as a transport probe. *J.Lab Clin.Med.* 96 (3):379-381, 1980.
102. G. Sachs, T. Berglindh, E. Rabon, B. Wallmark, M. L. Barcellona, H. B. Stewart, and G. Saccomani. The interaction of K+ with gastric parietal cells and gastric ATPase. *Ann.N.Y.Acad.Sci.* 358:118-137, 1980.
103. B. Wallmark, H. B. Stewart, E. Rabon, G. Saccomani, and G. Sachs. The catalytic cycle of gastric (H+ + K+)-ATPase. *J.Biol.Chem.* 255 (11):5313-5319, 1980.
104. L. D. Faller, D. H. Malinowska, E. Rabon, A. Smolka, and G. Sachs. Mechanistic studies of the gastric (H+ + K)-ATPase. *Prog.Clin.Biol.Res.* 73:153-174, 1981.
105. E. Fellenius, T. Berglindh, G. Sachs, L. Olbe, B. Elander, S. E. Sjostrand, and B. Wallmark. Substituted benzimidazoles inhibit gastric acid secretion by blocking (H+ + K+)ATPase. *Nature* 290 (5802):159-161, 1981.
106. A. Heinz, J. W. Jackson, B. E. Richey, G. Sachs, and J. A. Schafer. Amino Acid Transport and stimulation by substrates in the absence of a Na2+ electrochemical potential gradient. *J.Membr.Biol.* 62 (1-2):149-160, 1981.
107. A. Heinz, G. Sachs, and J. A. Schafer. Evidence for activation of an active electrogenic proton pump in Ehrlich ascites tumor cells during glycolysis. *J.Membr.Biol.* 61 (3):143-153, 1981.
108. H. R. Koelz, G. Sachs, and T. Berglindh. Cation effects on acid secretion in rabbit gastric glands. *Am.J.Physiol* 241 (5):G431-G442, 1981.
109. D. H. Malinowska, H. R. Koelz, S. J. Hersey, and G. Sachs. Properties of the gastric proton pump in unstimulated permeable gastric glands. *Proc.Natl.Acad.Sci.U.S.A* 78 (9):5908-5912, 1981.
110. T. P. Pretlow, H. B. Stewart, G. Sachs, T. G. Pretlow, and A. M. Pitts. Free-flow electrophoresis of an ascites mast-cell tumour. *Br.J.Cancer* 43 (4):537-541, 1981.
111. E. C. Rabon and G. Sachs. Thallium interaction with the gastric (K, H)-ATPase. *J.Membr.Biol.* 62 (1-2):19-27, 1981.
112. G. Saccomani, M. L. Barcellona, and G. Sachs. Reactivity of gastric (H+ + K+)-ATPase to N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline. *J.Biol.Chem.* 256 (23):12405-12410, 1981.
113. G. Saccomani, G. Sachs, J. Cuppoletti, and C. Y. Jung. Target molecular weight of the gastric (H+ + K+)-ATPase functional and structural molecular size. *J.Biol.Chem.* 256 (15):7727-7729, 1981.

114. G. Sachs and G. Makhlouf. Simple epithelia: fragments, cell vesicles. *Fed.Proc.* 40 (10):2441-2442, 1981.
115. B. Stewart, B. Wallmark, and G. Sachs. The interaction of H+ and K+ with the partial reactions of gastric (H+ + K+)-ATPase. *J.Biol.Chem.* 256 (6):2682-2690, 1981.
116. J. T. Tarvin, G. Sachs, and C. S. Pace. Glucose-induced electrical activity in pancreatic beta-cell: modulation by pH. *Am.J.Physiol* 241 (5):C264-C268, 1981.
117. C. Burnham, C. Munzesheimer, E. Rabon, and G. Sachs. Ion pathways in renal brush border membranes. *Biochim.Biophys.Acta* 685 (3):260-272, 1982.
118. L. Faller, R. Jackson, D. Malinowska, E. Mukidjam, E. Rabon, G. Saccomani, G. Sachs, and A. Smolka. Mechanistic aspects of gastric (H+ + K+)-ATPase. *Ann.N.Y.Acad.Sci.* 402:146-163, 1982.
119. C. Graves and G. Sachs. Quantitation of corneal endothelial potentials using a carbocyanine dye. *Biochim.Biophys.Acta* 685 (1):27-31, 1982.
120. R. J. Jackson and G. Sachs. Identification of gastric cyclic AMP binding proteins. *Biochim.Biophys.Acta* 717 (3):453-458, 1982.
121. H. Knauf, R. Lubcke, W. Kreutz, and G. Sachs. Interrelationships of ion transport in rat submaxillary duct epithelium. *Am.J.Physiol* 242 (2):F132-F139, 1982.
122. H. R. Koelz, S. J. Hersey, G. Sachs, and C. S. Chew. Pepsinogen release from isolated gastric glands. *Am.J.Physiol* 243 (3):G218-G225, 1982.
123. C. S. Pace and G. Sachs. Glucose-induced proton uptake in secretory granules of beta-cells in monolayer culture. *Am.J.Physiol* 242 (5):C382-C387, 1982.
124. E. Rabon, G. Sachs, S. Mardh, and B. Wallmark. ATP/ADP exchange activity of gastric (H+ +K+)-ATPase. *Biochim.Biophys.Acta* 688 (2):515-524, 1982.
125. E. C. Rabon, T. L. McFall, and G. Sachs. The gastric [H,K]ATPase:H+/ATP stoichiometry. *J.Biol.Chem.* 257 (11):6296-6299, 1982.
126. G. Sachs, L. D. Faller, and E. Rabon. Proton/hydroxyl transport in gastric and intestinal epithelia. *J.Membr.Biol.* 64 (3):123-135, 1982.
127. L. D. Faller, E. Rabon, and G. Sachs. Vanadate binding to the gastric H,K-ATPase and inhibition of the enzyme's catalytic and transport activities. *Biochemistry* 22 (20):4676-4685, 1983.
128. R. J. Jackson, J. Mendlein, and G. Sachs. Interaction of fluorescein isothiocyanate with the (H+ + K+)-ATPase. *Biochim.Biophys.Acta* 731 (1):9-15, 1983.
129. D. H. Malinowska, J. Cuppoletti, and G. Sachs. Cl- requirement of acid secretion in isolated gastric glands. *Am.J.Physiol* 245 (4):G573-G581, 1983.
130. S. B. Miller, G. Saccomani, T. P. Pretlow, P. M. Kimball, J. A. Scott, G. Sachs, and T. G. Pretlow. Purification of cells from livers of carcinogen-treated rats by free-flow electrophoresis. *Cancer Res.* 43 (9):4176-4179, 1983.
131. A. Smolka, H. F. Helander, and G. Sachs. Monoclonal antibodies against gastric H+ + K+ ATPase. *Am.J.Physiol* 245 (4):G589-G596, 1983.
132. B. Wallmark, G. Sachs, S. Mardh, and E. Fellenius. Inhibition of gastric (H+ + K+)-ATPase by the substituted benzimidazole, picoprazole. *Biochim.Biophys.Acta* 728 (1):31-38, 1983.
133. J. Cuppoletti and G. Sachs. Regulation of gastric acid secretion via modulation of a chloride conductance. *J.Biol.Chem.* 259 (23):14952-14959, 1984.
134. W. B. Im, D. P. Blakeman, J. Mendlein, and G. Sachs. Inhibition of (H+ + K+)-ATPase and H+ accumulation in hog gastric membranes by trifluoperazine, verapamil and 8-(N,N-diethylamino)octyl-3,4,5-trimethoxybenzoate. *Biochim.Biophys.Acta* 770 (1):65-72, 1984.
135. S. Muallem and G. Sachs. Changes in cytosolic free Ca2+ in isolated parietal cells. Differential effects of secretagogues. *Biochim.Biophys.Acta* 805 (2):181-185, 1984.
136. S. Muallem, D. Blissard, and G. Sachs. Single cell recording of quin 2 fluorescence. *Prog.Clin.Biol.Res.* 168:151-157, 1984.

137. B. E. Peerce, A. Smolka, and G. Sachs. Isolation of pepsinogen granules from rabbit gastric mucosa. *J.Biol.Chem.* 259 (14):9255-9262, 1984.
138. S. J. Hersey, G. Sachs, and D. K. Kasbekar. Acid secretion by frog gastric mucosa is electroneutral. *Am.J.Physiol* 248 (2 Pt 1):G246-G250, 1985.
139. W. B. Im, D. P. Blakeman, and G. Sachs. Reversal of antisecretory activity of omeprazole by sulfhydryl compounds in isolated rabbit gastric glands. *Biochim.Biophys.Acta* 845 (1):54-59, 1985.
140. J. D. Kaunitz, R. D. Gunther, and G. Sachs. Characterization of an electrogenic ATP and chloride-dependent proton translocating pump from rat renal medulla. *J.Biol.Chem.* 260 (21):11567-11573, 1985.
141. S. Muallem, M. Schoeffield, S. Pandol, and G. Sachs. Inositol trisphosphate modification of ion transport in rough endoplasmic reticulum. *Proc.Natl.Acad.Sci.U.S.A* 82 (13):4433-4437, 1985.
142. S. Muallem, C. Burnham, D. Blissard, T. Berglindh, and G. Sachs. Electrolyte transport across the basolateral membrane of the parietal cells. *J.Biol.Chem.* 260 (11):6641-6653, 1985.
143. S. Muallem and G. Sachs. Ca2+ metabolism during cholinergic stimulation of acid secretion. *Am.J.Physiol* 248 (2 Pt 1):G216-G228, 1985.
144. S. J. Pandol, M. S. Schoeffield, G. Sachs, and S. Muallem. Role of free cytosolic calcium in secretagogue-stimulated amylase release from dispersed acini from guinea pig pancreas. *J.Biol.Chem.* 260 (18):10081-10086, 1985.
145. S. J. Pandol, M. W. Thomas, M. S. Schoeffield, G. Sachs, and S. Muallem. Role of calcium in cholecystokinin-stimulated phosphoinositide breakdown in exocrine pancreas. *Am.J.Physiol* 248 (5 Pt 1):G551-G560, 1985.
146. E. Rabon, R. D. Gunther, A. Soumarmon, S. Bassilian, M. Lewin, and G. Sachs. Solubilization and reconstitution of the gastric H,K-ATPase. *J.Biol.Chem.* 260 (18):10200-10207, 1985.
147. J. D. Kaunitz and G. Sachs. Identification of a vanadate-sensitive potassium-dependent proton pump from rabbit colon. *J.Biol.Chem.* 261 (30):14005-14010, 1986.
148. S. Muallem, C. J. Fimmel, S. J. Pandol, and G. Sachs. Regulation of free cytosolic Ca2+ in the peptic and parietal cells of the rabbit gastric gland. *J.Biol.Chem.* 261 (6):2660-2667, 1986.
149. E. Rabon, M. Wilke, G. Sachs, and G. Zampighi. Crystallization of the gastric H,K-ATPase. *J.Biol.Chem.* 261 (3):1434-1439, 1986.
150. J. Cuppoletti, D. ures-Fischer, and G. Sachs. The lysosomal H+ pump: 8-azido-ATP inhibition and the role of chloride in H+ transport. *Biochim.Biophys.Acta* 899 (2):276-284, 1987.
151. W. B. Im, J. P. Davis, D. P. Blakeman, G. Sachs, and A. Robert. Gastric antisecretory activity of cycloheximide due to inhibition of protein synthesis. *Biochim.Biophys.Acta* 899 (2):285-294, 1987.
152. P. Lorentzon, R. Jackson, B. Wallmark, and G. Sachs. Inhibition of (H+ + K+)-ATPase by omeprazole in isolated gastric vesicles requires proton transport. *Biochim.Biophys.Acta* 897 (1):41-51, 1987.
153. S. Ueda, D. D. Loo, and G. Sachs. Regulation of K+ channels in the basolateral membrane of Necturus oxyntic cells. *J.Membr.Biol.* 97 (1):31-41, 1987.
154. B. Wallmark, C. Briving, J. Fryklund, K. Munson, R. Jackson, J. Mendlein, E. Rabon, and G. Sachs. Inhibition of gastric H+,K+-ATPase and acid secretion by SCH 28080, a substituted pyridyl(1,2a)imidazole. *J.Biol.Chem.* 262 (5):2077-2084, 1987.
155. L. A. Wheeler, G. Sachs, Vries G. De, D. Goodrum, E. Woldemussie, and S. Muallem. Manoalide, a natural sesterterpenoid that inhibits calcium channels. *J.Biol.Chem.* 262 (14):6531-6538, 1987.
156. G. L. Fain, A. Smolka, M. C. Cilluffo, M. J. Fain, D. A. Lee, N. C. Brecha, and G. Sachs. Monoclonal antibodies to the H+-K+ ATPase of gastric mucosa selectively stain the non-pigmented cells of the rabbit ciliary body epithelium. *Invest Ophthalmol.Vis.Sci.* 29 (5):785-794, 1988.
157. S. J. Hersey, L. Steiner, J. Mendlein, E. Rabon, and G. Sachs. SCH28080 prevents omeprazole inhibition of the gastric H+/K+-ATPase. *Biochim.Biophys.Acta* 956 (1):49-57, 1988.
158. S. J. Hersey, L. Steiner, S. Matheravidathu, and G. Sachs. Gastric H+-K+-ATPase in situ: relation to secretory state. *Am.J.Physiol* 254 (6 Pt 1):G856-G863, 1988.

159. P. Lorentzon, G. Sachs, and B. Wallmark. Inhibitory effects of cations on the gastric H+, K+ -ATPase. A potential-sensitive step in the K+ limb of the pump cycle. *J.Biol.Chem.* 263 (22):10705-10710, 1988.
160. D. H. Malinowska, G. Sachs, and J. Cuppoletti. Gastric H+ secretion: histamine (cAMP-mediated) activation of protein phosphorylation. *Biochim.Biophys.Acta* 972 (1):95-109, 1988.
161. S. Muallem, D. Blissard, E. J. Cragoe, Jr., and G. Sachs. Activation of the Na+/H+ and Cl-/. *J.Biol.Chem.* 263 (29):14703-14711, 1988.
162. K. B. Munson and G. Sachs. Inactivation of H+,K+-ATPase by a K+-competitive photoaffinity inhibitor. *Biochemistry* 27 (11):3932-3938, 1988.
163. E. C. Rabon, Im W. Bin, and G. Sachs. Preparation of gastric H+,K+-ATPase. *Methods Enzymol.* 157:649-654, 1988.
164. G. Sachs. Peptide regulation of acid secretion. *Annu.Rev.Physiol* 50:17-18, 1988.
165. J. R. Demarest, D. D. Loo, and G. Sachs. Activation of apical chloride channels in the gastric oxyntic cell. *Science* 245 (4916):402-404, 1989.
166. H. F. Helander, D. Anderson, K. G. Helander, A. Smolka, and G. Sachs. Immunocytochemical studies of gastric H+,K+-ATPase in the developing rat. *Scand.J.Gastroenterol.* 24 (7):863-869, 1989.
167. S. J. Hersey, A. Perez, S. Matheravidathu, and G. Sachs. Gastric H+-K+-ATPase in situ: evidence for compartmentalization. *Am.J.Physiol* 257 (4 Pt 1):G539-G547, 1989.
168. P. Lorentzon, S. J. Hersey, B. Wallmark, and G. Sachs. Ion permeability and pump regulation. *Ann.N.Y.Acad.Sci.* 574:134-144, 1989.
169. J. Mendlein and G. Sachs. The substitution of calcium for magnesium in H+,K+-ATPase catalytic cycle. Evidence for two actions of divalent cations. *J.Biol.Chem.* 264 (31):18512-18519, 1989.
170. A. Perez, D. Blissard, G. Sachs, and S. J. Hersey. Evidence for a chloride conductance in secretory membrane of parietal cells. *Am.J.Physiol* 256 (2 Pt 1):G299-G305, 1989.
171. C. Polvani, G. Sachs, and R. Blostein. Sodium ions as substitutes for protons in the gastric H,K-ATPase. *J.Biol.Chem.* 264 (30):17854-17859, 1989.
172. A. Smolka, G. Sachs, and P. Lorentzon. Cell-free synthesis of rat and rabbit gastric proton pump. *Gastroenterology* 97 (4):873-881, 1989.
173. J. Fryklund, K. Gedda, D. Scott, G. Sachs, and B. Wallmark. Coupling of H(+)-K(+)-ATPase activity and glucose oxidation in gastric glands. *Am.J.Physiol* 258 (5 Pt 1):G719-G727, 1990.
174. M. H. Garner, A. Bahador, and G. Sachs. Nonenzymatic glycation of Na,K-ATPase. Effects on ATP hydrolysis and K+ occlusion. *J.Biol.Chem.* 265 (25):15058-15066, 1990.
175. K. Hall, G. Perez, D. Anderson, C. Gutierrez, K. Munson, S. J. Hersey, J. H. Kaplan, and G. Sachs. Location of the carbohydrates present in the HK-ATPase vesicles isolated from hog gastric mucosa. *Biochemistry* 29 (3):701-706, 1990.
176. E. A. Mayer, D. D. Loo, W. J. Snape, Jr., and G. Sachs. The activation of calcium and calcium-activated potassium channels in mammalian colonic smooth muscle by substance P. *J.Physiol* 420:47-71, 1990.
177. J. Mendlein, M. L. Ditmars, and G. Sachs. Calcium binding to the H+,K(+)-ATPase. Evidence for a divalent cation site that is occupied during the catalytic cycle. *J.Biol.Chem.* 265 (26):15590-15598, 1990.
178. J. Mendlein and G. Sachs. Interaction of a K(+)-competitive inhibitor, a substituted imidazo[1,2a] pyridine, with the phospho- and dephosphoenzyme forms of H+, K(+)-ATPase. *J.Biol.Chem.* 265 (9):5030-5036, 1990.
179. S. Muallem, M. Khademazad, and G. Sachs. The route of Ca2+ entry during reloading of the intracellular Ca2+ pool in pancreatic acini. *J.Biol.Chem.* 265 (4):2011-2016, 1990.
180. C. H. Pedemonte, G. Sachs, and J. H. Kaplan. An intrinsic membrane glycoprotein with cytosolically oriented n-linked sugars. *Proc.Natl.Acad.Sci.U.S.A* 87 (24):9789-9793, 1990.
181. E. C. Rabon, S. Bassilian, G. Sachs, and S. J. Karlish. Conformational transitions of the H,K-ATPase studied with sodium ions as surrogates for protons. *J.Biol.Chem.* 265 (32):19594-19599, 1990.

182. M. A. Reuben, L. S. Lasater, and G. Sachs. Characterization of a beta subunit of the gastric H+/K(+)-transporting ATPase. *Proc.Natl.Acad.Sci.U.S.A* 87 (17):6767-6771, 1990.
183. G. Sachs, D. Scott, and M. Reuben. Omeprazole and the gastric mucosa. *Digestion* 47 Suppl 1:35-38, 1990.
184. G. Sachs and D. Scott. Cell digestion and genotoxicity assessment in gastric mucosa. *Digestion* 47 Suppl 1:31-34, 1990.
185. G. Sachs, E. Rabon, and S. J. Karlish. Transport studies by optical methods. *Methods Enzymol.* 191:469-479, 1990.
186. D. Scott, M. Reuben, G. Zampighi, and G. Sachs. Cell isolation and genotoxicity assessment in gastric mucosa. *Dig.Dis.Sci.* 35 (10):1217-1225, 1990.
187. L. A. Wheeler, D. D. Goodrum, and G. Sachs. Role of protein kinase C in the regulation of cytosolic Ca2+ in A431 cells: separation of growth factor and bradykinin pathways. *J.Membr.Biol.* 118 (1):77-91, 1990.
188. H. Zhao, P. A. Loessberg, G. Sachs, and S. Muallem. Regulation of intracellular Ca2+ oscillation in AR42J cells. *J.Biol.Chem.* 265 (34):20856-20862, 1990.
189. K. Hall, G. Perez, G. Sachs, and E. Rabon. Identification of H+/K(+)-ATPase alpha,beta-heterodimers. *Biochim.Biophys.Acta* 1077 (2):173-179, 1991.
190. J. D. Horisberger, P. Jaunin, M. A. Reuben, L. S. Lasater, D. C. Chow, J. G. Forte, G. Sachs, B. C. Rossier, and K. Geering. The H,K-ATPase beta-subunit can act as a surrogate for the beta-subunit of Na,K-pumps. *J.Biol.Chem.* 266 (29):19131-19134, 1991.
191. M. Maeda, K. Oshiman, S. Tamura, S. Kaya, S. Mahmood, M. A. Reuben, L. S. Lasater, G. Sachs, and M. Futai. The rat H+/K(+)-ATPase beta subunit gene and recognition of its control region by gastric DNA binding protein. *J.Biol.Chem.* 266 (32):21584-21588, 1991.
192. E. A. Mayer, X. P. Sun, S. Supplisson, A. Kodner, M. Regoli, and G. Sachs. Neurokinin receptor-mediated regulation of [Ca]i and Ca-sensitive ion channels in mammalian colonic muscle. *Ann.N.Y.Acad.Sci.* 632:439-441, 1991.
193. S. Muallem, P. Loessberg, G. Sachs, and L. A. Wheeler. Agonist-sensitive and -insensitive intracellular Ca2+ pools. Separate Ca(2+)-releasing mechanisms revealed by manoalide and benzohydroquinone. *Biochem.J.* 279 (Pt 2):367-375, 1991.
194. K. B. Munson, C. Gutierrez, V. N. Balaji, K. Ramnarayan, and G. Sachs. Identification of an extracytoplasmic region of H+,K(+)-ATPase labeled by a K(+)-competitive photoaffinity inhibitor. *J.Biol.Chem.* 266 (28):18976-18988, 1991.
195. E. Rabon, G. Sachs, S. Bassilian, C. Leach, and D. Keeling. A K(+)-competitive fluorescent inhibitor of the H,K-ATPase. *J.Biol.Chem.* 266 (19):12395-12401, 1991.
196. S. Supplisson, D. D. Loo, and G. Sachs. Diversity of K+ channels in the basolateral membrane of resting Necturus oxyntic cells. *J.Membr.Biol.* 123 (3):209-221, 1991.
197. A. Tari, V. Wu, M. Sumii, G. Sachs, and J. H. Walsh. Regulation of rat gastric H+/K(+)-ATPase alpha-subunit mRNA by omeprazole. *Biochim.Biophys.Acta* 1129 (1):49-56, 1991.
198. J. M. Wilkes, M. Kajimura, D. R. Scott, S. J. Hersey, and G. Sachs. Muscarinic responses of gastric parietal cells. *J.Membr.Biol.* 122 (2):97-110, 1991.
199. J. M. Wilkes, D. R. Scott, S. J. Hersey, and G. Sachs. Second messengers in the gastric gland: a focus on calcium. *Scand.J.Gastroenterol.Suppl* 180:70-84, 1991.
200. K. Bamberg, F. Mercier, M. A. Reuben, Y. Kobayashi, K. B. Munson, and G. Sachs. cDNA cloning and membrane topology of the rabbit gastric H+/K(+)-ATPase alpha-subunit. *Biochim.Biophys.Acta* 1131 (1):69-77, 1992.
201. D. Bayle, J. C. Robert, K. Bamberg, F. Benkouka, A. M. Cheret, M. J. Lewin, G. Sachs, and A. Soumarmon. Location of the cytoplasmic epitope for a K(+)-competitive antibody of the (H+,K+)-ATPase. *J.Biol.Chem.* 267 (27):19060-19065, 1992.

202. M. Besancon, J. M. Shin, F. Mercier, K. Munson, E. Rabon, S. Hersey, and G. Sachs. Chemomechanical coupling in the gastric H,K ATPase. *Acta Physiol Scand.Suppl* 607:77-88, 1992.
203. M. Kajimura, M. A. Reuben, and G. Sachs. The muscarinic receptor gene expressed in rabbit parietal cells is the m3 subtype. *Gastroenterology* 103 (3):870-875, 1992.
204. E. A. Mayer, A. Kodner, X. P. Sun, J. Wilkes, D. Scott, and G. Sachs. Spatial and temporal patterns of intracellular calcium in colonic smooth muscle. *J.Membr.Biol.* 125 (2):107-118, 1992.
205. E. C. Rabon, G. Sachs, C. A. Leach, and D. Keeling. A K+ competitive, conformational probe of the H,K-ATPase. *Acta Physiol Scand.Suppl* 607:269-273, 1992.
206. D. R. Scott, K. Munson, N. Modyanov, and G. Sachs. Determination of the sidedness of the C-terminal region of the gastric H,K-ATPase alpha subunit. *Biochim.Biophys.Acta* 1112 (2):246-250, 1992.
207. X. P. Sun, S. Supplisson, R. Torres, G. Sachs, and E. Mayer. Characterization of large-conductance chloride channels in rabbit colonic smooth muscle. *J.Physiol* 448:355-382, 1992.
208. M. Besancon, J. M. Shin, F. Mercier, K. Munson, M. Miller, S. Hersey, and G. Sachs. Membrane topology and omeprazole labeling of the gastric H+,K(+)-adenosinetriphosphatase. *Biochemistry* 32 (9):2345-2355, 1993.
209. C. Prinz, M. Kajimura, D. R. Scott, F. Mercier, H. F. Helander, and G. Sachs. Histamine secretion from rat enterochromaffinlike cells. *Gastroenterology* 105 (2):449-461, 1993.
210. D. R. Scott, H. F. Helander, S. J. Hersey, and G. Sachs. The site of acid secretion in the mammalian parietal cell. *Biochim.Biophys.Acta* 1146 (1):73-80, 1993.
211. J. M. Shin, M. Besancon, A. Simon, and G. Sachs. The site of action of pantoprazole in the gastric H+/K(+)-ATPase. *Biochim.Biophys.Acta* 1148 (2):223-233, 1993.
212. S. Supplisson, D. D. Loo, and G. Sachs. Whole-cell currents in isolated resting Necturus gastric oxynticopeptic cells. *J.Physiol* 463:57-82, 1993.
213. A. Tari, G. Yamamoto, K. Sumii, M. Sumii, Y. Takehara, K. Haruma, G. Kajiyama, V. Wu, G. Sachs, and J. H. Walsh. Role of histamine2 receptor in increased expression of rat gastric H(+)-K(+)-ATPase alpha-subunit induced by omeprazole. *Am.J.Physiol* 265 (4 Pt 1):G752-G758, 1993.
214. K. Bamberg and G. Sachs. Topological analysis of H+,K(+)-ATPase using in vitro translation. *J.Biol.Chem.* 269 (24):16909-16919, 1994.
215. K. Bamberg, S. Nylander, K. G. Helander, L. G. Lundberg, G. Sachs, and H. F. Helander. In situ hybridization of mRNA for the gastric H+,K(+)-ATPase in rat oxyntic mucosa. *Biochim.Biophys.Acta* 1190 (2):355-359, 1994.
216. A. Cheng-Bennett, M. F. Chan, G. Chen, T. Gac, M. E. Garst, C. Gluchowski, L. J. Kaplan, C. E. Protzman, M. B. Roof, G. Sachs, and . Studies on a novel series of acyl ester prodrugs of prostaglandin F2 alpha. *Br.J.Ophthalmol.* 78 (7):560-567, 1994.
217. J. L. Edelman, M. Kajimura, E. Woldemussie, and G. Sachs. Differential effects of carbachol on calcium entry and release in CHO cells expressing the m3 muscarinic receptor. *Cell Calcium* 16 (3):181-193, 1994.
218. J. L. Edelman, G. Sachs, and J. S. Adorante. Ion transport asymmetry and functional coupling in bovine pigmented and nonpigmented ciliary epithelial cells. *Am.J.Physiol* 266 (5 Pt 1):C1210-C1221, 1994.
219. C. Prinz, D. R. Scott, D. Hurwitz, H. F. Helander, and G. Sachs. Gastrin effects on isolated rat enterochromaffin-like cells in primary culture. *Am.J.Physiol* 267 (4 Pt 1):G663-G675, 1994.
220. C. Prinz, G. Sachs, J. H. Walsh, D. H. Coy, and S. V. Wu. The somatostatin receptor subtype on rat enterochromaffinlike cells. *Gastroenterology* 107 (4):1067-1074, 1994.
221. M. Reuben, L. Rising, C. Prinz, S. Hersey, and G. Sachs. Cloning and expression of the rabbit gastric CCK-A receptor. *Biochim.Biophys.Acta* 1219 (2):321-327, 1994.
222. D. R. Scott, M. Besancon, G. Sachs, and H. Helander. Effects of antisecretory agents on parietal cell structure and H/K-ATPase levels in rabbit gastric mucosa in vivo. *Dig.Dis.Sci.* 39 (10):2118-2126, 1994.

243. N. Zeng, J. H. Walsh, T. Kang, S. V. Wu, and G. Sachs. Peptide YY inhibition of rat gastric enterochromaffin-like cell function. *Gastroenterology* 112 (1):127-135, 1997.
244. D. Bayle, S. Wangler, T. Weitzenegger, W. Steinhilber, J. Volz, M. Przybylski, K. P. Schafer, G. Sachs, and K. Melchers. Properties of the P-type ATPases encoded by the copAP operons of *Helicobacter pylori* and Helicobacter felis. *J.Bacteriol.* 180 (2):317-329, 1998.
245. J. A. Kraut, J. Hiura, J. M. Shin, A. Smolka, G. Sachs, and D. Scott. The Na(+)-K(+)-ATPase beta 1 subunit is associated with the HK alpha 2 protein in the rat kidney. *Kidney Int.* 53 (4):958-962, 1998.
246. N. Lambrecht, Z. Corbett, D. Bayle, S. J. Karlish, and G. Sachs. Identification of the site of inhibition by omeprazole of a alpha-beta fusion protein of the H,K-ATPase using site-directed mutagenesis. *J.Biol.Chem.* 273 (22):13719-13728, 1998.
247. K. Melchers, L. Herrmann, F. Mauch, D. Bayle, D. Heuermann, T. Weitzenegger, A. Schuhmacher, G. Sachs, R. Haas, G. Bode, K. Bensch, and K. P. Schafer. Properties and function of the P type ion pumps cloned from *Helicobacter pylori. Acta Physiol Scand.Suppl* 643:123-135, 1998.
248. D. Melle-Milovanovic, M. Milovanovic, S. Nagpal, G. Sachs, and J. M. Shin. Regions of association between the alpha and the beta subunit of the gastric H,K-ATPase. *J.Biol.Chem.* 273 (18):11075-11081, 1998.
249. M. Rektorschek, D. Weeks, G. Sachs, and K. Melchers. Influence of pH on metabolism and urease activity of *Helicobacter pylori. Gastroenterology* 115 (3):628-641, 1998.
250. G. Sachs. Symposium on ion motive ATPases. Introduction. *Acta Physiol Scand.Suppl* 643:5-6, 1998.
251. D. R. Scott, D. Weeks, C. Hong, S. Postius, K. Melchers, and G. Sachs. The role of internal urease in acid resistance of *Helicobacter pylori. Gastroenterology* 114 (1):58-70, 1998.
252. Y. Wen, J. L. Edelman, T. Kang, N. Zeng, and G. Sachs. Two functional forms of vascular endothelial growth factor receptor-2/Flk-1 mRNA are expressed in normal rat retina. *J.Biol.Chem.* 273 (4):2090-2097, 1998.
253. N. Zeng, T. Kang, R. M. Lyu, H. Wong, Y. Wen, J. H. Walsh, G. Sachs, and J. R. Pisegna. The pituitary adenylate cyclase activating polypeptide type 1 receptor (PAC1-R) is expressed on gastric ECL cells: evidence by immunocytochemistry and RT-PCR. *Ann.N.Y.Acad.Sci.* 865:147-156, 1998.
254. N. Zeng, T. Kang, Y. Wen, H. Wong, J. Walsh, and G. Sachs. Galanin inhibition of enterochromaffin-like cell function. *Gastroenterology* 115 (2):330-339, 1998.
255. A. T. Beggah, P. Beguin, K. Bamberg, G. Sachs, and K. Geering. beta-subunit assembly is essential for the correct packing and the stable membrane insertion of the H,K-ATPase alpha-subunit. *J.Biol.Chem.* 274 (12):8217-8223, 1999.
256. C. Gatto, S. Lutsenko, J. M. Shin, G. Sachs, and J. H. Kaplan. Stabilization of the H,K-ATPase M5M6 membrane hairpin by K+ ions. Mechanistic significance for p2-type atpases. *J.Biol.Chem.* 274 (20):13737-13740, 1999.
257. S. Hallen, M. Branden, P. A. Dawson, and G. Sachs. Membrane insertion scanning of the human ileal sodium/bile acid co-transporter. *Biochemistry* 38 (35):11379-11388, 1999.
258. G. Sachs and T. J. Humphries. Rabeprazole: pharmacology, pharmacokinetics, and potential for drug interactions. Introduction. *Aliment.Pharmacol.Ther.* 13 Suppl 3:1-2, 1999.
259. Y. Wen, J. L. Edelman, T. Kang, and G. Sachs. Lipocortin V may function as a signaling protein for vascular endothelial growth factor receptor-2/Flk-1. *Biochem.Biophys.Res.Commun.* 258 (3):713-721, 1999.
260. N. Zeng, C. Athmann, T. Kang, J. H. Walsh, and G. Sachs. Role of neuropeptide-sensitive L-type Ca(2+) channels in histamine release in gastric enterochromaffin-like cells. *Am.J.Physiol* 277 (6 Pt 1):G1268-G1280, 1999.
261. N. Zeng, C. Athmann, T. Kang, R. M. Lyu, J. H. Walsh, G. V. Ohning, G. Sachs, and J. R. Pisegna. PACAP type I receptor activation regulates ECL cells and gastric acid secretion. *J.Clin.Invest* 104 (10):1383-1391, 1999.

223. J. M. Shin, M. Kajimura, J. M. Arguello, J. H. Kaplan, and G. Sachs. Biochemical identification of transmembrane segments of the Ca(2+)-ATPase of sarcoplasmic reticulum. *J.Biol.Chem.* 269 (36):22533-22537, 1994.
224. J. M. Shin and G. Sachs. Identification of a region of the H,K-ATPase alpha subunit associated with the beta subunit. *J.Biol.Chem.* 269 (12):8642-8646, 1994.
225. A. Tari, G. Yamamoto, Y. Yonei, M. Sumii, K. Sumii, K. Haruma, G. Kajiyama, V. Wu, G. Sachs, and J. H. Walsh. Effect of histamine on rat gastric H(+)-K(+)-ATPase alpha-subunit expression. *Am.J.Physiol.* 266 (3 Pt 1):G444-G450, 1994.
226. D. Bayle, D. Weeks, and G. Sachs. The membrane topology of the rat sarcoplasmic and endoplasmic reticulum calcium ATPases by in vitro translation scanning. *J.Biol.Chem.* 270 (43):25678-25684, 1995.
227. J. L. Edelman, D. D. Loo, and G. Sachs. Characterization of potassium and chloride channels in the basolateral membrane of bovine nonpigmented ciliary epithelial cells. *Invest Ophthalmol.Vis.Sci.* 36 (13):2706-2716, 1995.
228. K. Gedda, D. Scott, M. Besancon, P. Lorentzon, and G. Sachs. Turnover of the gastric H+,K(+)-adenosine triphosphatase alpha subunit and its effect on inhibition of rat gastric acid secretion. *Gastroenterology* 109 (4):1134-1141, 1995.
229. J. Geibel, R. Abraham, I. Modlin, and G. Sachs. Gastrin-stimulated changes in Ca2+ concentration in parietal cells depends on adenosine 3',5'-cyclic monophosphate levels. *Gastroenterology* 109 (4):1060-1067, 1995.
230. J. A. Kraut, F. Starr, G. Sachs, and M. Reuben. Expression of gastric and colonic H(+)-K(+)-ATPase in the rat kidney. *Am.J.Physiol* 268 (4 Pt 2):F581-F587, 1995.
231. G. Sachs. Progress in therapy of ulcer disease. *Bildgebung* 62 Suppl 1:76, 1995.
232. N. M. Vladimirova, N. A. Potapenko, G. Sachs, and N. N. Modyanov. Determination of the sidedness of the carboxy-terminus of the Na+/K(+)ATPase alpha-subunit using lactoperoxidase iodination. *Biochim.Biophys.Acta* 1233 (2):175-184, 1995.
233. K. G. Helander, K. Bamberg, G. Sachs, D. Melle, and H. F. Helander. Localization of mRNA for the muscarinic M1 receptor in rat stomach. *Biochim.Biophys.Acta* 1312 (2):158-162, 1996.
234. D. D. Loo, G. Sachs, and C. Prinz. Potassium and chloride currents in rat gastric enterochromaffin-like cells. *Am.J.Physiol* 270 (5 Pt 1):E739-E745, 1996.
235. A. Matin, E. Zychlinsky, M. Keyhan, and G. Sachs. Capacity of *Helicobacter pylori* to generate ionic gradients at low pH is similar to that of bacteria which grow under strongly acidic conditions. *Infect.Immun.* 64 (4):1434-1436, 1996.
236. K. Melchers, T. Weitzenegger, A. Buhmann, W. Steinhilber, G. Sachs, and K. P. Schafer. Cloning and membrane topology of a P type ATPase from *Helicobacter pylori. J.Biol.Chem.* 271 (1):446-457, 1996.
237. K. Meyer-Rosberg, D. R. Scott, D. Rex, K. Melchers, and G. Sachs. The effect of environmental pH on the proton motive force of *Helicobacter pylori. Gastroenterology* 111 (4):886-900, 1996.
238. J. M. Shin and G. Sachs. Dimerization of the gastric H+, K(+)-ATPase. *J.Biol.Chem.* 271 (4):1904-1908, 1996.
239. N. Zeng, J. H. Walsh, T. Kang, K. G. Helander, H. F. Helander, and G. Sachs. Selective ligand-induced intracellular calcium changes in a population of rat isolated gastric endocrine cells. *Gastroenterology* 110 (6):1835-1846, 1996.
240. D. Bayle, D. Weeks, and G. Sachs. Identification of membrane insertion sequences of the rabbit gastric cholecystokinin-A receptor by in vitro translation. *J.Biol.Chem.* 272 (32):19697-19707, 1997.
241. M. Besancon, A. Simon, G. Sachs, and J. M. Shin. Sites of reaction of the gastric H,K-ATPase with extracytoplasmic thiol reagents. *J.Biol.Chem.* 272 (36):22438-22446, 1997.
242. J. A. Kraut, J. Hiura, M. Besancon, A. Smolka, G. Sachs, and D. Scott. Effect of hypokalemia on the abundance of HK alpha 1 and HK alpha 2 protein in the rat kidney. *Am.J.Physiol* 272 (6 Pt 2):F744-F750, 1997.

262. C. Athmann, N. Zeng, D. R. Scott, and G. Sachs. Regulation of parietal cell calcium signaling in gastric glands. *Am.J.Physiol Gastrointest.Liver Physiol* 279 (5):G1048-G1058, 2000.
263. C. Athmann, N. Zeng, T. Kang, E. A. Marcus, D. R. Scott, M. Rektorschek, A. Buhmann, K. Melchers, and G. Sachs. Local pH elevation mediated by the intrabacterial urease of *Helicobacter pylori* cocultured with gastric cells. *J.Clin.Invest* 106 (3):339-347, 2000.
264. S. Hallen, J. Fryklund, and G. Sachs. Inhibition of the human sodium/bile acid cotransporters by side-specific methanethiosulfonate sulfhydryl reagents: substrate-controlled accessibility of site of inactivation. *Biochemistry* 39 (22):6743-6750, 2000.
265. W. Hong, S. Morimatsu, T. Goto, G. Sachs, D. R. Scott, D. L. Weeks, T. Kohno, C. Morita, T. Nakano, Y. Fujioka, and K. Sano. Contrast-enhanced immunoelectron microscopy for *Helicobacter pylori*. *J.Microbiol.Methods* 42 (2):121-127, 2000.
266. N. Lambrecht, K. Munson, O. Vagin, and G. Sachs. Comparison of covalent with reversible inhibitor binding sites of the gastric H,K-ATPase by site-directed mutagenesis. *J.Biol.Chem.* 275 (6):4041-4048, 2000.
267. K. B. Munson, N. Lambrecht, and G. Sachs. Effects of mutations in M4 of the gastric H+,K+-ATPase on inhibition kinetics of SCH28080. *Biochemistry* 39 (11):2997-3004, 2000.
268. J. R. Pisegna, G. V. Ohning, C. Athmann, N. Zeng, J. H. Walsh, and G. Sachs. Role of PACAP1 receptor in regulation of ECL cells and gastric acid secretion by pituitary adenylate cyclase activating peptide. *Ann.N.Y.Acad.Sci.* 921:233-241, 2000.
269. M. Rektorschek, A. Buhmann, D. Weeks, D. Schwan, K. W. Bensch, S. Eskandari, D. Scott, G. Sachs, and K. Melchers. Acid resistance of *Helicobacter pylori* depends on the UreI membrane protein and an inner membrane proton barrier. *Mol.Microbiol.* 36 (1):141-152, 2000.
270. D. Scott, D. Weeks, K. Melchers, and G. Sachs. UreI-mediated urea transport in *Helicobacter pylori*: an open and shut case? *Trends Microbiol.* 8 (8):348-349, 2000.
271. D. R. Scott, E. A. Marcus, D. L. Weeks, A. Lee, K. Melchers, and G. Sachs. Expression of the *Helicobacter pylori* ureI gene is required for acidic pH activation of cytoplasmic urease. *Infect.Immun.* 68 (2):470-477, 2000.
272. D. L. Weeks, S. Eskandari, D. R. Scott, and G. Sachs. A H+-gated urea channel: the link between *Helicobacter pylori* urease and gastric colonization. *Science* 287 (5452):482-485, 2000.
273. Y. Wen, G. Sachs, and C. Athmann. A novel lens epithelium gene, LEP503, is highly conserved in different vertebrate species and is developmentally regulated in postnatal rat lens. *Exp.Eye Res.* 70 (2):159-168, 2000.
274. D. F. Woodward, A. H. Krauss, J. Chen, D. W. Gil, K. M. Kedzie, C. E. Protzman, L. Shi, R. Chen, H. A. Krauss, A. Bogardus, H. T. Dinh, L. A. Wheeler, S. W. Andrews, R. M. Burk, T. Gac, M. B. Roof, M. E. Garst, L. J. Kaplan, G. Sachs, K. L. Pierce, J. W. Regan, R. A. Ross, and M. F. Chan. Replacement of the carboxylic acid group of prostaglandin f(2alpha) with a hydroxyl or methoxy substituent provides biologically unique compounds. *Br.J.Pharmacol.* 130 (8):1933-1943, 2000.
275. M. Zizak, M. E. Cavet, D. Bayle, C. M. Tse, S. Hallen, G. Sachs, and M. Donowitz. Na(+)/H(+) exchanger NHE3 has 11 membrane spanning domains and a cleaved signal peptide: topology analysis using in vitro transcription/translation. *Biochemistry* 39 (27):8102-8112, 2000.
276. N. Bell, M. D. Karol, G. Sachs, P. Greski-Rose, D. E. Jennings, and R. H. Hunt. Duration of effect of lansoprazole on gastric pH and acid secretion in normal male volunteers. *Aliment.Pharmacol.Ther.* 15 (1):105-113, 2001.
277. J. A. Kraut, K. G. Helander, H. F. Helander, N. D. Iroezi, E. A. Marcus, and G. Sachs. Detection and localization of H+-K+-ATPase isoforms in human kidney. *Am.J.Physiol Renal Physiol* 281 (4):F763-F768, 2001.

278. J. M. Shin, R. Goldshleger, K. B. Munson, G. Sachs, and S. J. Karlish. Selective Fe2+-catalyzed oxidative cleavage of gastric H+,K+-ATPase: implications for the energy transduction mechanism of P-type cation pumps. *J.Biol.Chem.* 276 (51):48440-48450, 2001.
279. O. Vagin, K. Munson, N. Lambrecht, S. J. Karlish, and G. Sachs. Mutational analysis of the K+-competitive inhibitor site of gastric H,K-ATPase. *Biochemistry* 40 (25):7480-7490, 2001.
280. D. L. Weeks and G. Sachs. Sites of pH regulation of the urea channel of *Helicobacter pylori*. *Mol.Microbiol.* 40 (6):1249-1259, 2001.
281. Y. Wen, N. Ibaraki, V. N. Reddy, and G. Sachs. Functional analysis of the promoter and chromosomal localization for human LEP503, a novel lens epithelium gene. *Gene* 269 (1-2):61-71, 2001.
282. B. A. Berkowitz and G. Sachs. Life Cycle of a Block Buster Drug: Discovery and Development of Omeprazole (PrilosecTM). *Mol.Intervent.* 2 (1):6-11, 2002.
283. S. Hallen, A. Bjorquist, A. M. Ostlund-Lindqvist, and G. Sachs. Identification of a region of the ileal-type sodium/bile acid cotransporter interacting with a competitive bile acid transport inhibitor. *Biochemistry* 41 (50):14916-14924, 2002.
284. S. Hallen, O. Mareninova, M. Branden, and G. Sachs. Organization of the membrane domain of the human liver sodium/bile acid cotransporter. *Biochemistry* 41 (23):7253-7266, 2002.
285. N. Kim, D. L. Weeks, J. M. Shin, D. R. Scott, M. K. Young, and G. Sachs. Proteins released by *Helicobacter pylori* in vitro. *J.Bacteriol.* 184 (22):6155-6162, 2002.
286. M. Mollenhauer-Rektorschek, G. Hanauer, G. Sachs, and K. Melchers. Expression of UreI is required for intragastric transit and colonization of gerbil gastric mucosa by *Helicobacter pylori*. *Res.Microbiol.* 153 (10):659-666, 2002.
287. G. Patchornik, K. Munson, R. Goldshleger, A. Shainskaya, G. Sachs, and S. J. Karlish. The ATP-Mg2+ binding site and cytoplasmic domain interactions of Na+,K+-ATPase investigated with Fe2+-catalyzed oxidative cleavage and molecular modeling. *Biochemistry* 41 (39):11740-11749, 2002.
288. D. R. Scott, E. A. Marcus, D. L. Weeks, and G. Sachs. Mechanisms of acid resistance due to the urease system of *Helicobacter pylori*. *Gastroenterology* 123 (1):187-195, 2002.
289. J. M. Shin and G. Sachs. Restoration of acid secretion following treatment with proton pump inhibitors. *Gastroenterology* 123 (5):1588-1597, 2002.
290. O. Vagin, S. Denevich, K. Munson, and G. Sachs. SCH28080, a K+-competitive inhibitor of the gastric H,K-ATPase, binds near the M5-6 luminal loop, preventing K+ access to the ion binding domain. *Biochemistry* 41 (42):12755-12762, 2002.
291. P. Voland, D. L. Weeks, D. Vaira, C. Prinz, and G. Sachs. Specific identification of three low molecular weight membrane-associated antigens of *Helicobacter pylori*. *Aliment.Pharmacol.Ther.* 16 (3):533-544, 2002.
292. W. Hong, K. Sano, S. Morimatsu, D. R. Scott, D. L. Weeks, G. Sachs, T. Goto, S. Mohan, F. Harada, N. Nakajima, and T. Nakano. Medium pH-dependent redistribution of the urease of *Helicobacter pylori*. *J.Med.Microbiol.* 52 (Pt 3):211-216, 2003.
293. K. Munson, O. Vagin, G. Sachs, and S. Karlish. Molecular modeling of SCH28080 binding to the gastric H,K-ATPase and MgATP interactions with S. *Ann.N.Y.Acad.Sci.* 986:106-110, 2003.
294. D. Pantoflickova, D. R. Scott, G. Sachs, G. Dorta, and A. L. Blum. 13C urea breath test (UBT) in the diagnosis of *Helicobacter pylori*: why does it work better with acid test meals? *Gut* 52 (7):933-937, 2003.
295. S. Tatishchev, N. Abuladze, A. Pushkin, D. Newman, W. Liu, D. Weeks, G. Sachs, and I. Kurtz. Identification of membrane topography of the electrogenic sodium bicarbonate cotransporter pNBC1 by in vitro transcription/translation. *Biochemistry* 42 (3):755-765, 2003.
296. O. Vagin, S. Denevich, and G. Sachs. Plasma membrane delivery of the gastric H,K-ATPase: the role of beta-subunit glycosylation. *Am.J.Physiol Cell Physiol* 285 (4):C968-C976, 2003.

297. O. Vagin, K. Munson, S. Denevich, and G. Sachs. Inhibition kinetics of the gastric H,K-ATPase by K-competitive inhibitor SCH28080 as a tool for investigating the luminal ion pathway. *Ann.N.Y.Acad.Sci.* 986:111-115, 2003.
298. P. Voland, D. L. Weeks, E. A. Marcus, C. Prinz, G. Sachs, and D. Scott. Interactions among the seven *Helicobacter pylori* proteins encoded by the urease gene cluster. *Am.J.Physiol Gastrointest.Liver Physiol* 284 (1):G96-G106, 2003.
299. Y. Wen, E. A. Marcus, U. Matrubutham, M. A. Gleeson, D. R. Scott, and G. Sachs. Acid-adaptive genes of *Helicobacter pylori*. *Infect.Immun.* 71 (10):5921-5939, 2003.
300. N. Kim, E. A. Marcus, Y. Wen, D. L. Weeks, D. R. Scott, H. C. Jung, I. S. Song, and G. Sachs. Genes of *Helicobacter pylori* regulated by attachment to AGS cells. *Infect.Immun.* 72 (4):2358-2368, 2004.
301. A. Schafermeyer, M. Gratzl, R. Rad, A. Dossumbekova, G. Sachs, and C. Prinz. Isolation and receptor profiling of ileal enterochromaffin cells. *Acta Physiol Scand.* 182 (1):53-62, 2004.
302. J. M. Shin, Y. M. Cho, and G. Sachs. Chemistry of covalent inhibition of the gastric (H+, K+)-ATPase by proton pump inhibitors. *J.Am.Chem.Soc.* 126 (25):7800-7811, 2004.
303. O. Vagin, S. Turdikulova, and G. Sachs. The H,K-ATPase {beta} Subunit as a Model to Study the Role of N-Glycosylation in Membrane Trafficking and Apical Sorting. *J.Biol.Chem.* 279 (37):39026-39034, 2004.
304. D. L. Weeks, G. Gushansky, D. R. Scott, and G. Sachs. Mechanism of proton gating of a urea channel. *J.Biol.Chem.* 279 (11):9944-9950, 2004.
305. J. M. Shin and G. Sachs. Differences in binding properties of two proton pump inhibitors on the gastric H+,K+, -ATPase in vivo. *Biochemical Pharmacology.* Dec 1;68(11):2117-27, 2004.
306. E. A. Marcus, A. P. Moshfegh, G. Sachs, and D. R. Scott. The Periplasmic α-Carbonic Anhydrase Activity of *Helicobacter pylori* Is Essential for Acid Acclimation. *J. Bacteriol.* Jan;187(2):729-738, 2005.
307. D. S. Oh, S. N. Lieu, D. J. Yamaguchi, K. Tachiki, N. Lambrecht, G.V. Ohning, G. Sachs, P.M. Germano and J. R. Pisegna. PACAP Regulation of Secretion and Proliferation of Pure Populations of Gastric ECL Cells. *J Mol Neurosci.* 26(1):85-98, 2005.
308. C. S. Spada, A. H. Krauss, D. F. Woodward, J. Chen, C. E. Protzman, A. L. Nieves, L. A. Wheeler, D. R. Scott, and G. Sachs. Bimatoprost and prostaglandin F(2alpha) selectively stimulate intracellular calcium signaling in different cat iris sphincter cells. *Exp Eye Res.* Jan;80(1):135-145, 2005.
309. N. W. Lambrecht, I. Yakubov, D. Scott, and G. Sachs. Identification of the K efflux channel coupled to the gastric H,K ATPase during acid secretion. *Physiol Genomics.* Mar 21;21(1) 81-91, 2005. [Epub 2004 Dec 21].
310. K. Munson, R. Garcia, and G. Sachs. Inhibitor and Ion Binding Sites on the Gastric H,K-ATPase. *Biochemistry.* Apr 12;44(14):5267-84, 2005.
311. J. A. Kraut and G. Sachs. Hartnup Disorder Unraveling the mystery. *Trends Pharm Sci.* 26;53-55, 2005.
312. O. Vagin, S. Turdikulova, I. Yakubov, and G. Sachs. Use of the H,K-ATPase beta subunit to identify multiple sorting pathways for plasma membrane delivery in polarized cells. *J Biol Chem.* Apr 15;280(15):14741-54, 2005. [Epub 2005 Feb 4].
313. A. Diller, O. Vagin, G. Sachs and H. J. Apell. Electrogenic partial reactions of the gastric H,K-ATPase. *Biophys J.* May;88(5):3348-59, 2005. [Epub 2005 Mar 4].

Submitted or In Press (Manuscripts Peer-Reviewed):

1. J.M. Shin, G. Grrundler J. Senn-Bilfinger and G. Sachs. Functional consequences of the oligomeric form of the membrane-bound gastric H,K,-ATPase. *Biochemistry* (in press).
2. O. Mareninova, J. M. Shin, O. Vagin, S. Turdikulova, S. Hallen and G. Sachs. The Topography of the Membrane Domain of the Liver Na^{+}-dependent Bile Acid Transporter. *Biochemistry* (in press).

3. O. Vagin, S. Turdikulova and G. Sachs. Recombinant addition of N-glycosylation sites to the basolateral NaK beta1 subunit results in its clustering in the caveolae and apical sorting in HGT-1 cells. *J Biol. Chem.* (in press).

Reviews:

1. G. Sachs. H+ transport by a non-electrogenic gastric ATPase as a model for acid secretion. *Rev.Physiol Biochem.Pharmacol.* 79:133-162, 1977.
2. G. Sachs, J. G. Spenney, and W. S. Rehm. Gastric secretion. *Int.Rev.Physiol* 12:127-171, 1977.
3. G. Sachs, J. G. Spenney, and M. Lewin. H+ transport: regulation and mechanism in gastric mucosa and membrane vesicles. *Physiol Rev.* 58 (1):106-173, 1978.
4. G. Sachs. H+ pathways and pH changes in gastric tissue. *Gastroenterology.* 75:750-753, 1978.
5. G. Sachs, R. J. Jackson, and E. C. Rabon. Use of plasma membrane vesicles. *Am.J.Physiol* 238 (3):G151-G164, 1980.
6. G. Sachs, T. Berglindh, E. Rabon, H. B. Stewart, M. L. Barcellona, B. Wallmark, and G. Saccomani. Aspects of parietal cell biology: cells and vesicles. *Ann.N.Y.Acad.Sci.* 341:312-334, 1980.
7. H. R. Koelz, S. A. Muller-Lissner, D. H. Malinowska, and G. Sachs. The stomach and duodenum. *The Gastroenterology Annual.* Vol. 1:37-78, 1983.
8. E. Rabon, J. Cuppoletti, D. Malinowska, A. Smolka, H. F. Helander, J. Mendlein, and G. Sachs. Proton secretion by the gastric parietal cell. *J.Exp.Biol.* 106:119-133, 1983.
9. D. H. Malinowska and G. Sachs. Cellular mechanisms of acid secretion. *Clin.Gastroenterol.* 13 (2):309-326, 1984.
10. G. Sachs. Pump blockers and ulcer disease. *N. Engl. J. Med.* 310:785-786, 1984.
11. T. Berglindh and G. Sachs. Emerging strategies in ulcer therapy: pumps and receptors. *Scand.J.Gastroenterol.Suppl* 108:7-14, 1985.
12. G. Sachs. The parietal cell as a therapeutic target. *Scand.J.Gastroenterol.Suppl* 118:1-10, 1986.
13. G. Sachs, S. Muallem, and S. J. Hersey. Passive and active transport in the parietal cell. *Comp Biochem.Physiol A* 90 (4):727-731, 1988.
14. G. Sachs, E. Carlsson, P. Lindberg, and B. Wallmark. Gastric H,K-ATPase as therapeutic target. *Annu.Rev.Pharmacol.Toxicol.* 28:269-284, 1988.
15. P. Lorentzon, D. Scott, S. Hersey, B. Wallmark, E. Rabon, and G. Sachs. The gastric H+,K+-ATPase. *Prog.Clin.Biol.Res.* 273:247-254, 1988.
16. G. Sachs, K. Munson, V. N. Balaji, D. ures-Fischer, S. J. Hersey, and K. Hall. Functional domains of the gastric HK ATPase. *J.Bioenerg.Biomembr.* 21 (5):573-588, 1989.
17. G. Sachs and S. Fleischer. Transport machinery: an overview. *Methods Enzymol.* 171:3-12, 1989.
18. G. Sachs and S. Muallem. Sites and mechanisms of Ca2+ movement in non-excitable cells. *Cell Calcium* 10 (5):265-273, 1989.
19. G. Sachs and B. Wallmark. Biological basis of omeprazole therapy. *J.Gastroenterol.Hepatol.* 4 Suppl 2:7-18, 1989.
20. G. Sachs and B. Wallmark. The gastric H+,K+-ATPase: the site of action of omeprazole. *Scand.J.Gastroenterol.Suppl* 166:3-11, 1989.
21. G. Sachs. Therapeutic control of acid secretion. *Current opinions in Gastroenterology.* 6:859-866, 1990.
22. G. Sachs, K. Munson, K. Hall, and S. J. Hersey. Gastric H+,K(+)-ATPase as a therapeutic target in peptic ulcer disease. *Dig.Dis.Sci.* 35 (12):1537-1544, 1990.
23. S. Muallem, H. Zhao, E. Mayer, and G. Sachs. Regulation of intracellular calcium in epithelial cells. *Semin.Cell Biol.* 1 (4):305-310, 1990.
24. B. Wallmark, P. Lorentzon, and G. Sachs. The gastric H+,K(+)-ATPase. *J.Intern.Med.Suppl* 732:3-8, 1990.

25. G. Sachs and K. Munson. Mammalian phosphorylating ion-motive ATPases. *Curr.Opin.Cell Biol.* 3 (4):685-694, 1991.
26. J. M. Wilkes, D. R. Scott, S. J. Hersey, and G. Sachs. Second messengers in the gastric gland, a focus on calcium. *Scand.J.Gastroenterology.Suppl.* 180:70-84, 1991.
27. G. Sachs, J. M. Shin, M. Besancon, K. Munson, and S. Hersey. Topology and sites in the H,K-ATPase. *Ann.N.Y.Acad.Sci.* 671:204-216, 1992.
28. C. Prinz, M. Kajimura, D. Scott, H. Helander, J. Shin, M. Besancon, K. Bamberg, S. Hersey, and G. Sachs. Acid secretion and the H,K ATPase of stomach. *Yale J.Biol.Med.* 65 (6):577-596, 1992.
29. A. J. Pope and G. Sachs. Reversible inhibitors of the gastric (H+/K+)-ATPase as both potential therapeutic agents and probes of pump function. *Biochem.Soc.Trans.* 20 (3):566-572, 1992.
30. G. Sachs, M. Besancon, J. M. Shin, F. Mercier, K. Munson, and S. Hersey. Structural aspects of the gastric H,K-ATPase. *J.Bioenerg.Biomembr.* 24 (3):301-308, 1992.
31. G. Sachs, J. M. Shin, M. Besancon, and C. Prinz. The continuing development of gastric acid pump inhibitors. *Aliment.Pharmacol.Ther.* 7 Suppl 1:4-12, discussion, 1993.
32. D. R. Scott, S. J. Hersey, C. Prinz, and G. Sachs. Actions of Antiulcer Drugs. *Pharm.Sci.* 1453-1454, 1993.
33. G. Sachs, C. Prinz, D. Loo, K. Bamberg, M. Besancon, and J. M. Shin. Gastric acid secretion: activation and inhibition. *Yale J.Biol.Med.* 67 (3-4):81-95, 1994.
34. J. M. Shin, M. Besancon, C. Prinz, A. Simon, and G. Sachs. Continuing development of acid pump inhibitors: site of action of pantoprazole. *Aliment.Pharmacol.Ther.* 8 Suppl 1:11-23, 1994.
35. R. Huber, B. Kohl, G. Sachs, J. Senn-Bilfinger, W. A. Simon, and E. Sturm. Review article: the continuing development of proton pump inhibitors with particular reference to pantoprazole. *Aliment.Pharmacol.Ther.* 9 (4):363-378, 1995.
36. B. I. Hirschowitz, D. Keeling, M. Lewin, S. Okabe, M. Parsons, K. Sewing, B. Wallmark, and G. Sachs. Pharmacological aspects of acid secretion. *Dig.Dis.Sci.* 40 (2 Suppl):3S-23S, 1995.
37. R. Hunt and G. Sachs. A review of the status of omeprazole: the Hambury workshop. *Dig.Dis.Sci.* 40 (2 Suppl):1S-2S, 1995.
38. S. J. Hersey and G. Sachs. Gastric acid secretion. *Physiol Rev.* 75 (1):155-189, 1995.
39. G. Sachs, J. M. Shin, C. Briving, B. Wallmark, and S. Hersey. The pharmacology of the gastric acid pump: the H+,K+ ATPase. *Annu.Rev.Pharmacol.Toxicol.* 35:277-305, 1995.
40. G. Sachs, K. Meyer-Rosberg, D. R. Scott, and K. Melchers. Acid, protons and *Helicobacter pylori*. *Yale J.Biol.Med.* 69 (3):301-316, 1996.
41. G. Sachs and C. Prinz. Gastric Enterochromaffin-like Cells and the Regulation of Acid Secretion. *News in Physiological Sciences.* 11:57-62, 1996.
42. G. Sachs, J. M. Shin, K. Bamberg, and C. Prinz. Gastric Acid Secretion: The H,K ATPase and Ulcer Disease. *Molecular Biology of Membrane Transport Disorders.* 469-483, 1996.
43. J. M. Shin, M. Besancon, K. Bamberg, and G. Sachs. Structural aspects of the gastric H,K ATPase. *Ann.N.Y.Acad.Sci.* 834:65-76, 1997.
44. G. Sachs, K. Meyer-Rosberg, D. R. Scott, K. Melchers, J. Shin, and M. Besancon. Acid secretion and *Helicobacter pylori*. *Digestion* 58 Suppl 1:8-13, 1997.
45. G. Sachs, N. Zeng, and C. Prinz. Physiology of isolated gastric endocrine cells. *Annu.Rev.Physiol* 59:243-256, 1997.
46. D. Bayle, D. Weeks, S. Hallen, K. Melchers, K. Bamberg, and G. Sachs. In vitro translation analysis of integral membrane proteins. *J.Recept.Signal.Transduct.Res.* 17 (1-3):29-56, 1997.
47. G. Sachs. Proton pump inhibitors and acid-related diseases. *Pharmacotherapy* 17 (1):22-37, 1997.
48. D. Melle-Milovanovic, N. Lambrecht, G. Sachs, and J. M. Shin. Structural aspects of the gastric H,K ATPase: the M5/M6 domain and alpha beta association. *Acta Physiol Scand.Suppl* 643:147-162, 1998.

49. G. Sachs, J. M. Shin, M. Besancon, N. Lambrecht, D.R. Scott, D.L. Weeks, D. Melle, and K. Melchers. What is to be expected in acid related disorders: Acid Control and *Helicobacter pylori*. *World Congress of GI.* Vienna, John Libbey Eurotext Limited, Publishers, 1998.
50. G. Sachs. Gastrointestinal Physiology. *Annual Rev of Physiol.* March, Vol. 51, 81-82, 1998.
51. D. Scott, D. Weeks, K. Melchers, and G. Sachs. The life and death of *Helicobacter pylori*. *Gut* 43 Suppl 1:S56-S60, 1998.
52. J. M. Shin, D. B. Bayle, K. Bamberg, G. Sachs. The Gastric H,K ATPase. *Biomembranes.* 5:185-224, 1998.
53. N. Zeng and G. Sachs. Properties of isolated gastric enterochromaffin-like cells. *Yale J.Biol.Med.* 71 (3-4):233-246, 1998.
54. G. Sachs. Acid inhibition and gastroesophageal reflux disease. *Yale J.Biol.Med.* 72 (2-3):227-229, 1999.
55. G. Sachs, D. Scott, D. Weeks, and K. Melchers. Gastric habitation by *Helicobacter pylori*: insights into acid adaptation. *Trends Pharmacol.Sci.* 21 (11):413-416, 2000.
56. G. Sachs, J. M. Shin, K. Munson, O. Vagin, N. Lambrecht, D. R. Scott, D. L. Weeks, and K. Melchers. Review article: the control of gastric acid and *Helicobacter pylori* eradication. *Aliment.Pharmacol.Ther.* 14 (11):1383-1401, 2000.
57. K. Munson, N. Lambrecht, J. M. Shin, and G. Sachs. Analysis of the membrane domain of the gastric H(+)/K(+)-ATPase. *J.Exp.Biol.* 203 Pt 1:161-170, 2000.
58. M. M. Wolfe and G. Sachs. Acid suppression: optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. *Gastroenterology* 118 (2 Suppl 1):S9-31, 2000.
59. G. Sachs. Improving on PPI-based therapy of GORD. *Eur.J.Gastroenterol.Hepatol.* 13 Suppl 1:S35-S41, 2001.
60. G. Sachs, J. M. Shin, O. Vagin, K. Munson, D. Weeks, D. R. Scott, and P. Voland. Current trends in the treatment of upper gastrointestinal disease. *Best.Pract.Res.Clin.Gastroenterol.* 16 (6):835-849, 2002.
61. G. Sachs, J. M. Shin, V. Pratha, and D. Hogan. Synthesis or rupture: duration of acid inhibition by proton pump inhibitors. *Drugs Today (Barc.)* 39 Suppl A:11-14, 2003.
62. G. Sachs. Physiology of the parietal cell and therapeutic implications. *Pharmacotherapy* 23 (10 Pt 2):68S-73S, 2003.
63. G. Sachs, D. L. Weeks, K. Melchers, and D. R. Scott. The gastric biology of *Helicobacter pylori*. *Annu.Rev.Physiol* 65:349-369, 2003.
64. G. Sachs and J. M. Shin. The basis of differentiation of PPIs. *Drugs Today (Barc.)* 40 Suppl A:9-14, 2004.

Submitted or In Press (Reviews):

1. J. M. Shin and G. Sachs. The Gastric H,K-ATPase as a Drug Target. *J Dig Dis and Sciences* (in press).
2. J. M. Shin and G. Sachs. Acid Dependent Lesions of the Upper Gastrointestinal Tract. *Enc Comp Medic Chem II.* Vol. 6 (in press).
3. G. Sachs, D. L. Weeks, Y. Wen, K. Melchers, E. A. Marcus and D. R. Scott. Acid Acclimation by *Helicobacter pylori*. *Physiology* (in press).
4. J.M Shin and G. Sachs. The Gastric H,K-ATPase as a Drug Target. *J. Dig. Dis. and Sci* (in press).
5. G. Sachs, J. M. Shin, K. B. Munson, O. Vagin, Y. M. Cho, I. Yabukov, N. Lambrecht, J. Senn-Bilfinger. Insights into Control of Gastric Acid Secretion from Structure-Function Analysis of the Gastric H,K ATPase (in press).

Chapters in Books:

1. A. L. Blum, B. I. Hirschowitz, H. F. Helander, and G. Sachs. Electrical coupling and conductive shunts in necturus gastric mucosa. Gastric Secretion (G. Sachs, E. Heinz, and K.J. Ullrich eds.). New York: Academic Press. 165-180, 1972.
2. V. D. Wiebelhaus, A. L. Blum, and G. Sachs. Isolation of oxyntic cell. Methods in Enzymology (S. Fleischer and L. Packer eds.). Vol. 32, part B, 707-717, 1975.
3. G. Sachs. McGraw-Hill Yearbook of Science and Technology. McGraw-Hill, New York, 272-273, 1977.
4. G. Sachs. Ion Transport by gastric mucosa. Physiology of Membrane Disorders (T. E. Andreoli, J. F. Hoffman and D. D. Fanestil eds.). Vol. 29, New York: Plenum Press. 563-576, 1978.
5. E. Fellenius, T. Berglindh, A. Brandstorm, B. Elander, H. F. Helander, L. Olbe, G. Sachs, S. E. Sjostrand, and B. Wallmark. The inhibitory action of substituted benzimidazoles on isolated oxyntic glands and H+/K+ -ATPase. Hydrogen Ion Transport in Epithelia (I. Schulz, G. Sachs, J. G. Forte and K. J. Ulrich eds.). Elsevier/North Holland Biomedical Press, Amsterdam, 193-202, 1980.
6. R. Kinne and G. Sachs. Isolation and characterization of biological membranes. Physiology of Membrane Disorders (T. E. Andreoli, J. F. Hoffman and D. D. Fanestil eds.). Vol., Chapter 5, New York: Plenum Publishing Co. 75-95, 1986.
7. P. N. Maton, G. Sachs, and B. Wallmark. Therapeutic Use of Omeprazole in Man: Pharmacology, Efficacy, Toxity and Comparison with H2 Receptor Antagonists. Handbook of Pharmacology v. 99, 7:159-181, 1991.
8. J. M. Shin, K. Bamberg, M. L. Besancon, K. B. Munson, F. Mercier, D. Bayle, S. Hersey and G. Sachs. The Topology of the alpha-beta subunits of the Gastric H/K ATPase. Springer Verlag. NATO ASI Series. H89:35-53, 1994.
9. G. Sachs. The gastric H,K ATPase: Regulation and structure-function of the acid pump of the stomach. Physiology of the gastrointestinal tract (L. R. Johnson ed.). Vols. 1 and 2, 3rd Edn. Raven Press. 1119-1138, 1994.
10. Sachs. Acid Secretion. Gastroenterology and Hepatology: The Comprehensive Visual Reference, *Stomach and Duodenum Volume* (M. Feldman, M.D. volume ed.) Current Medicine. 1995.
11. D. R. Scott, D. L. Weeks, M. Rektorschek, G. Sachs, and K. Melchers. Physiological Aspects of *Helicobacter pylori*- Basic Mechanisms to Clinical Cure (R. H. Hunt and G. N. J. Tytgat ed.). Kluwer Academic Publishers, 1998.
12. G. Sachs, D. R. Scott, D. L. Weeks, M. Rektorschek, and K. Melchers. Physiologic Aspects of *Helicobacter pylori* and Acid Homeostasis. Proceedings of "Peptic Ulcer Disease- Perspectives, Understanding and Development." Hong Kong, JAMA Southeast Asia, 14:1-5, 1998.
13. D. L. Weeks, D. R. Scott, P. R. Voland, E. A. Marcus, C. Athmann, K. Melchers, and G. Sachs. The Urease system of *Helicobacter pylori*. Helicobacter 2000 (R. Hunt and G. Tytgat ed.). Kluwer Academic Publishers, 2000.
14. G. Sachs, C. Athmann, D. L. Weeks and D. R. Scott. Debate: Gastric consequences of proton pump inhibitor therapy and *Helicobacter pylori* eradication. Helicobacter 2000 (R. Hunt ed.). Kluwer Academic Publishers, 2000.
15. G. Sachs and D. Keeling. Ion Motive ATPase: V- and P-type ATPases. Encyclopedia of Life Sciences. Macmillan, 2000.
16. N. Zeng and G. Sachs. Neural Regulation of Gastric Endocrine Cells. Medical Publishers, 2002.
17. O. Vagin, K. Munson, J. M. Shin, N. Lambrecht, S. Karlish, and G. Sachs. The Gastric H,K ATPase. Kluwer Press, 2002.
18. J. M. Shin, B. Wallmark and G. Sachs. Proton Pump Inhibitors and Acid Pump Antagonists. Encyclopedic Reference of Molecular Pharmacology (S. Offermannand W. Rosental ed.). Springer-Verlag, Berlin, Germany, 2003.
19. J. M. Shin and G. Sachs. Proton Pump Inhibitors. Encyclopedia of Gastroenterology. 259-262, 2004.

20. J. M. Shin, O. Vagin, K. Munson, and G. Sachs. Gastric H+,K+ -ATPase. Handbook of ATPase: Biochemistry, Cell Biology, Pathophysiology (M. Futai, Y. Wada, and J. H. Kaplan ed.). WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim, 179-209, 2004.
21. J. M. Shin and G. Sachs. P-Type Pumps: H+/K+ Pump. Encyclopedia of Biological Chemistry. 3:565, 2004.

In Press (Chapter in Book):

1. J.M Shin and G. Sachs. The Gastric H,K-ATPase as a Drug Target. *Progress in Basic and Clinical Pharmacology*. Vol. 12, Karger Publishers.

Books:

2. G. Sachs and S.J. Hersey eds. The Gastric Parietal Cell: Its Clinical Relevance in the Management of Acid-Related Disorders. Ox Clin Com. 7-43, 1990.
3. G. Sachs, S. J. Hersey, and C. Prinz. Acid secretion Mystery to Mechanism. Shugar Press, 1993.
4. I. M. Modlin and G. Sachs. Acid related disease. Biology and Treatment. Schnetztor-Verlag GmbH, Konstanz, 1st Edn., 1988.
5. I. M. Modlin and G. Sachs. The logic of Omeprazole: Treatment by Design. CoMed Communications, Inc., Philadelphia, Pennsylvania, 2001.
6. I. M. Modlin and G. Sachs. Acid related disease. Biology and Treatment. Lippincott Williams & Wilkins, Philadelphia, Pennsylvania, 2nd Edn., 2004.

Letters:

1. G. Sachs and D. Scott. Omeprazole does not interact with DNA. *Mutagenesis* 7 (6):475-477, 1992.
2. D. R. Scott, S. J. Hersey, C. Prinz, and G. Sachs. Actions of antiulcer drugs. *Science* 262 (5138):1453-1454, 1993.
3. G. Sachs. The safety of omeprazole: true or false? *Gastroenterology* 106 (5):1400-1401, 1994.
4. G. Sachs. Omepraxole and ocular damage. Lack of causality holds true. *BMJ* 316 (7124):67-68, 1998.
5. G. Sachs, D. Scott, D. Weeks, and K. Melchers. The importance of the surface urease of *Helicobacter pylori*: fact or fiction? *Trends Microbiol.* 9 (11):532-534, 2001.
6. M. M. Wolfe, L. S. Welage, and G. Sachs. Proton pump inhibitors and gastric acid secretion. *Am.J.Gastroenterol.* 96 (12):3467-3468, 2001.
7. G. Sachs, D. Scott, D. Weeks, and K. Melchers. The compartment buffered by the urease of *Helicobacter pylori*: cytoplasm or periplasm? *Trends Microbiol.* 10 (5):217-218, 2002.

Editorials:

1. G. Sachs. H^+ pathways and pH changes in gastric tissue. *Gastroenterology* 75 (4):750-753, 1978.
2. G. Sachs. Pump blockers and ulcer disease. *N.Engl.J.Med.* 310 (12):785-786, 1984.
3. G. Sachs. Gastritis, *Helicobacter pylori*, and proton pump inhibitors. *Gastroenterology* 112 (3):1033-1036, 1997.

THIRTEENTH EDITION

HARRISON'S PRINCIPLES OF INTERNAL MEDICINE

Editors

KURT J. ISSELBACHER, A.B., M.D.
Mallinckrodt Professor of Medicine, Harvard Medical School; Physician and Director, Cancer Center, Massachusetts General Hospital, Boston

EUGENE BRAUNWALD, A.B., M.D., M.A. (Hon.), M.D. (Hon.)
Hersey Professor of the Theory and Practice of Physic, Harvard Medical School; Chairman, Department of Medicine, Brigham and Women's Hospital, Boston

JEAN D. WILSON, M.D.
Charles Cameron Sprague Distinguished Chair and Professor of Internal Medicine; Chief, Division of Endocrinology and Metabolism, The University of Texas Southwestern Medical Center, Dallas

JOSEPH B. MARTIN, M.D., Ph.D., F.R.C.P. (C), M.A. (Hon.)
Professor of Neurology and Chancellor, University of California, San Francisco

ANTHONY S. FAUCI, M.D.
Director, National Institute of Allergy and Infectious Diseases; Chief, Laboratory of Immunoregulation; Director, Office of AIDS Research, National Institutes of Health, Bethesda

DENNIS L. KASPER, M.D.
William Ellery Channing Professor of Medicine, Harvard Medical School; Chief, Division of Infectious Diseases, Beth Israel Hospital; Co-Director, Channing Laboratory, Brigham and Women's Hospital, Boston

McGRAW-HILL, Inc.
Health Professions Division

New York St. Louis San Francisco Colorado Springs Auckland Bogotá Caracas Hamburg Lisbon London Madrid Mexico Milan Montreal New Delhi Paris San Juan São Paulo Singapore Sydney Tokyo Toronto

Note: Dr. Fauci's work as editor and author was performed outside the scope of his employment as a U.S. government employee. This work represents his personal and professional views and not necessarily those of the U.S. government.

HARRISON'S
PRINCIPLES OF INTERNAL MEDICINE
Thirteenth Edition

1 2 3 4 5 6 7 8 9 0 DOW DOW 9 8 7 6 5 4

Foreign Language Editions
CHINESE (Twelfth Edition)—McGraw-Hill Book Company-Singapore, © 1994
FRENCH (Twelfth Edition)—Flammarion, © 1992
GERMAN (Tenth Edition)—Schwabe and Company, Ltd., © 1986
GREEK (Twelfth Edition)—Parissianos, © 1994 (est.)
ITALIAN (Twelfth Edition)—McGraw-Hill Libri Italia S.r.l. © 1992
JAPANESE (Eleventh Edition)—Hirokawa, © 1991
PORTUGUESE (Twelfth Edition)—Editora Guanabara Koogan, S.A., © 1992
SPANISH (Twelfth Edition)—McGraw-Hill/Interamericana de Espana, © 1992

This book was set in Times Roman by Monotype Composition Company. The editors were J. Dereck Jeffers and Stuart D. Boynton. The indexer was Irving Tullar; the production supervisor was Roger Kasunic; the designer was Marsha Cohen; R. R. Donnelley & Sons Company was printer and binder.

Library of Congress Cataloging-in-Publication Data

Harrison's principles of internal medicine—13th ed./editors,
Kurt J. Isselbacher . . . [et al.]
p. cm.
Includes bibliographical references and index.
ISBN 0-07-032370-4 (1-vol. ed.) : 98.00 — ISBN 0-07-911169-6 (2 vol. ed. set) : 127.00 — ISBN 0-07-032371-2 (bk. 1). — ISBN 0-07-032372-0 (bk. 2)
1. Internal medicine. I. Harrison, Tinsley Randolph, 1900– II. Isselbacher, Kurt J. III. Title: Principles of internal medicine.
[DNLM: 1. Internal Medicine. WB 115 P957 1994]
RC46.H333 1994
616—dc20
DNLM/DLC
for Library of Congress

93-47393
CIP

ments of serum iron, folate, and vitamin B_{12}. Iron or folate deficiency should be treated by oral replacement. Vitamin B_{12} deficiency should be treated with monthly intramuscular injections of the vitamin.

OSTEOMALACIA AND OSTEOPOROSIS Osteoporosis and osteomalacia are common after partial or complete gastrectomy but occur rarely after vagotomy with pyloroplasty. Osteomalacia is extremely frequent following gastrojejunostomy or Billroth II anastomosis. These bone changes are believed to result from malabsorption of calcium and vitamin D. Patients may develop bone pain and have pathologic fractures. The incidence of bone fractures in men following gastric resection has been estimated to be almost twice that of control subjects of similar age. Reduced bone density identified by x-ray requires years to develop. Patients with osteomalacia usually have increased levels of serum alkaline phosphatase and may have reduced serum calcium concentrations. These patients should be treated by supplemental oral vitamin D and calcium. The frequency of osteoporosis and osteomalacia after partial or complete gastrectomy is sufficiently great to justify treatment with vitamin D and calcium indefinitely, especially in females, following gastric resection.

GENERAL MALABSORPTION (See also Chap. 254) Mild, chemically demonstable steatorrhea is common in patients after ulcer surgery. Weight loss is more common after partial gastric resection (approximately 60 percent of patients) than with vagotomy without resection. The major cause of weight loss is reduced food intake. On a 100-g fat diet, loss of stool fat seldom exceeds 15 g/d (normal individuals less than 7 g/d). The causes of maldigestion and malabsorption after peptic ulcer surgery include rapid gastric emptying, reduced dispersion of food in the stomach, reduced bile concentrations in the gut lumen, increased rate of transit of the meal through the small intestine, and reduced or delayed pancreatic secretory responses to feeding. Steatorrhea and weight loss, sometimes accompanied by vitamin B_{12} malabsorption, may develop as a result of bacterial overgrowth, especially in patients with afferent loop bacterial stasis. Overt symptoms and other manifestations of malabsorption appearing after surgery for peptic ulcer also may be due to other preexisting conditions, including latent celiac sprue and chronic pancreatitis.

CARCINOMA AFTER PARTIAL GASTRECTOMY Several studies have documented an increased incidence of adenocarcinoma of the stomach in duodenal ulcer patients following partial gastric resection and after vagotomy and drainage without resection. This usually develops 10 or more years after ulcer surgery. The possibility of carcinoma of the stomach should be considered when abdominal symptoms, which may be similar to or distinct from those due to the original ulcer, appear many years after apparently successful surgery.

ZOLLINGER-ELLISON SYNDROME (GASTRINOMA)

In 1955, Zollinger and Ellison described the syndrome that bears their names, which consists of ulcer disease of the upper gastrointestinal tract, marked increases in gastric acid secretion, and non-beta islet cell tumors of the pancreas.

ETIOLOGY AND PATHOGENESIS Zollinger and Ellison, in their original description of the syndrome, suggested that the ulcer disease in these patients resulted from release of a secretagogue from these tumors into the circulation which accounted for the often enormously increased rates of gastric acid secretion. Their proposal proved correct when in 1960 extracts of Zollinger-Ellison (Z-E) tumors were shown to stimulate gastric acid secretion. Subsequently, it was found that these pancreatic islet cell tumors contained gastrin and that there were large amounts of this hormone in the circulation producing the pathophysiologic characteristics of the syndrome. These gastrin-containing tumors are therefore now called *gastrinomas*.

Gastrinomas have been reported most often within the pancreas. Pancreatic gastrinomas may vary in size from 1 mm to more than 20 cm in diameter. Multiple primary tumors are common. From one-half to two-thirds of patients have multiple gastrinomas. Pancreatic gastrinomas are most common in the head of the pancreas. In more than half of Zollinger-Ellison patients harboring gastrinomas the tumors cannot be identified at surgery. There is recent evidence that with careful search when gastrinomas are located they are found as frequently (or perhaps more frequently) in the wall of the duodenum as in the pancreas. Duodenal gastrinomas, approximately 50 percent of which are solitary, are usually found in the submucosa of the first or second parts of the duodenum. Gastrinomas also have been located less commonly in other sites, including the hilum of the spleen and rarely in the stomach. Gastrinomas have been found in lymph nodes in proximity to the pancreas, proximal duodenum, and spleen in the absence of demonstrated primary tumors. These probably represent local metastases from undiscovered duodenal wall gastrinomas. Approximately 90 percent of gastrinomas are found within an anatomic triangle (the gastrinoma triangle) which is comprised of the junction of the cystic and common bile ducts superiorly, the junction of the second and third portions of the duodenum inferiorly, and the junction of the pancreatic body and neck medially. In unusual instances, the Z-E syndrome has resulted from gastrinomas originating from remote organs, e.g., parathyroid and ovarian tumors. About two-thirds of gastrinomas are histologically or biologically malignant. Malignant gastrinomas usually grow slowly; however, a small portion may be rapidly invasive and may metastasize early and widely. Metastasis is most often to regional lymph nodes and liver; spread also may be to peritoneal surfaces, spleen, bone, skin, or mediastinum. Gastrinomas have light-microscopic similarities to carcinoid tumors and may be mistaken for these tumors, especially when gastrinomas arise from the mucosa of the small intestine or stomach. Pancreatic islet cell hyperplasia occurs in approximately 10 percent of patients with the Z-E syndrome. Hyperplasia of the islets, accompanying recognized or unidentified gastrinoma, appears to be an association or a consequence, rather than a cause, of excess gastrin release, since gastrin is not present in the hyperplastic tissue.

In an estimated 20 to 60 percent of patients with the Z-E syndrome the gastrinoma is a component of the multiple endocrine neoplasia type 1 (MEN 1) syndrome, an autosomal dominant disorder with a high degree of penetrance and great variability in expressivity. The MEN 1 locus is on chrosomome 11. Patients with MEN 1 may have clinically recognized hyperplasia, adenomas, or carcinoma involving, in order of frequency, the parathyroid glands, pancreatic islets, and pituitary. Hyperparathyroidism has been reported in 87 percent of patients with MEN 1 syndrome, and gastrinoma has been reported in approximately half of them (see Chap. 343). However, there is accumulating evidence that when carefully sought for there is probably involvement of all three organs in all patients with MEN 1, although it is frequently without overt clinical expression. Gastrinomas in non-MEN 1 patients are considered to be sporadic. Multiple gastrinomas are usually present in patients with MEN 1 and are usually smaller than sporadic gastrinomas. Gastrinomas with MEN 1 are located more frequently in the wall of the duodenum than in the pancreas. Patients, including those with duodenal gastrinomas, usually have multiple pancreatic islet cell tumors, most of which are not gastrinomas.

In most gastrinomas, approximately 80 to 95 percent of gastrin is in the form of heptadecapeptide gastrin (G-17), with most of the remainder being G-34. In contrast, approximately two-thirds of circulating gastrin in gastrinoma patients is G-34; most of the remainder is G-17. However, smaller amounts of even larger forms of gastrin and smaller gastrin fragments can be detected in the serum. When examined carefully, almost all gastrin-secreting islet cell tumors are found to contain multiple hormones that are usually clinically silent. These have included, among others, ACTH, glucagon, melanocyte-stimulating hormone, parathyroid hormone, growth hormone releasing factor (GRF), insulin, pancreatic polypeptide, and vasoactive intestinal peptide. Of these, ACTH is the most common; it is found in approximately 30 percent of gastrinomas. Cushing's syndrome with increased serum ACTH levels has been reported in 8 percent of 75 Z-E patients. ACTH-releasing gastrinomas are often aggressively malignant. In contrast, ACTH may be released by pituitary tumors in patients with MEN 1, in whom symptoms of Cushing's syndrome

are generally mild and gastrinomas are usually not metastatic. Approximately one-third of patients with gastrinomas have increases in serum concentrations of *pancreatic polypeptide*.

The parietal cell mass is substantially expanded to from three to six times normal secondary to the trophic effects of circulating gastrin on parietal cells. Small, multicentric, noninvasive carcinoid tumors have been identified in the gastric mucosa of patients with the Z-E syndrome. These tumors and associated focal areas of enterochromaffin-like (ECL) cell hyperplasia are believed to result from substantial and sustained hypergastrinemia. They also have been found in the gastric mucosa of patients with pernicious anemia and achlorhydria, who have striking increases in serum gastrin in the range of those found with gastrinoma.

While the true incidence of the Z-E syndrome is not known, estimates are that it accounts for 0.1 to 1 percent of peptic ulcers. The Z-E syndrome may occur at any age, but initial manifestations occur most commonly between the ages 30 and 60.

CLINICAL FEATURES From 90 to 95 percent of patients with gastrinomas develop ulceration of the gastrointestinal tract at some point during the course of their disease. Profound gastric acid hypersecretion is found in most, but not all, patients. Especially early in the course of the disease, symptoms are usually similar to those of patients with typical peptic ulcer. However, ulcer symptoms may be more fulminant, progressive, and persistent and, in general, respond poorly to usual medical and surgical peptic ulcer treatment programs. The anatomic site of the ulcers in patients with gastrinoma is similar, but not identical, to that of patients with common types of peptic ulcer. About 75 percent of gastrinoma patients have ulcers in the first portion of the duodenum or in the stomach; these are usually single but may be multiple. When multiple ulcers occur, they are frequently located not only in the first portion of the duodenum, the site of common duodenal ulcer, but also in the remainder of the duodenum or even the jejunum. In one large series, 14 percent of the ulcers were in the duodenum beyond its first portion and 11 percent in the jejunum.

Diarrhea occurs in about 40 percent of patients, and about 7 percent of patients with gastrinoma have diarrhea in the absence of ulcer disease. The diarrhea is due to the outpouring of large amounts of hydrochloric acid into the proximal duodenum and can be reduced or eliminated by aspiration of gastric juice. The excessive acid has been shown to reduce the pH of the contents of the proximal and distal jejunum to as low as 1 and 3.6, respectively. Inflammatory changes may be produced in the mucosa of the small intestine secondary to the injurious effect of large amounts of acid and pepsin. Steatorrhea, which is less common than diarrhea, results from inactivation of pancreatic lipase by large concentrations of acid in the proximal small intestine and from decreases in luminal bile acids. The decrease in intraluminal bile acid concentration is caused by precipitation of the major bile acids at low pH. This leads to impaired micelle formation, which, in turn, reduces intestinal absorption of fatty acids and monoglycerides (see Chap. 254). Vitamin B_{12} malabsorption, not correctable by addition of intrinsic factor, has been detected in some patients with the Z-E syndrome. Although gastric secretion of intrinsic factor appears normal, the reduced pH within the gut interferes with intrinsic factor–mediated vitamin B_{12} absorption. This can be corrected by neutralization of the intestinal contents. The mechanisms by which low pH in the gut interferes with intrinsic factor action is not known.

DIAGNOSIS The presence of gastrinoma should be suspected in patients with a compatible clinical history, especially in those with marked acid hypersecretion. More than 90 percent of gastrinoma patients have basal gastric acid outputs (BAO) that exceed 15 mmol/h. In some instances, the basal output may be greater than 150 mmol/h. However, there is substantial overlap in rates of gastric acid secretion among patients with gastrinoma, those with duodenal ulcer, and normal subjects. Gastrinoma patients often have BAO rates that are greater than 60 percent of those induced by maximal stimulation (MAO). In most normal subjects and duodenal ulcer patients, basal acid secretory rates are less than 60 percent of maximal secretion. However, because of frequent exceptions in patients with gastrinomas and common duodenal ulcers, the use of the BAO/MAO ratio is of no value in the certain identification of patients with gastrinoma.

Some radiographic features may suggest the diagnosis of the Z-E syndrome. Large mucosal folds may be demonstrated most prominently in the stomach but also in the duodenum and, in some instances, the jejunum. The lumen of the stomach and small intestine often contains large amounts of fluid. Radiographic features of most ulcers in these patients, except when they are distal in location, are similar to those of common peptic ulcer. Gastrinomas are difficult to localize. In almost half of patients with clinical and laboratory evidence, the tumors cannot be identified at surgery. Selective arteriography identifies gastrinomas in approximately one-third of patients with clinical and biochemical evidence of the Z-E syndrome. Computed tomography (CT) identifies gastrinomas in 30 percent and ultrasound in 15 percent of patients with the Z-E syndrome. Use of both selective arteriography and CT has been reported to identify 44 percent of gastrinomas in Z-E patients and 80 percent of those located at surgery. Endoscopic retrograde pancreaticoduodenography has not proved to be of assistance in the diagnosis or exclusion of pancreatic gastrinomas. A small number of duodenal wall gastrinomas have been identified and confirmed histologically by duodenoscopy.

The diagnosis in a patient with clinical features consistent with the Z-E syndrome depends on the demonstration of *increased serum gastrin levels* by radioimmunoassay. Fasting serum gastrin levels in normal subjects and patients with typical duodenal ulcer average approximately 20 to 50 pg/mL and usually do not exceed 150 pg/mL. Patients with gastrinoma almost always have fasting serum gastrin levels that are greater than 200 pg/mL and have been found as high as 450,000 pg/mL. Approximately half these patients have fasting serum gastrin levels that are less than 1000 pg/mL (an approximate mean value for serum gastrin for patients with gastrinoma).

Several provocative tests have been used to evaluate patients with possible gastrinoma, especially those who do not exhibit pronounced hypergastrinemia (i.e., serum gastrin > 1000 pg/mL). These tests utilize measurements of serum gastrin levels in response to intravenous secretin injection, calcium infusion, or ingestion of a standard test meal.

In the *secretin injection test*, secretin (Kabi secretin, 2 units per kilogram) is given intravenously over 30 to 60 s. Gastrin is measured in serum samples obtained immediately before injection of secretin, at 2 and 5 min after secretin, and at 5-min intervals thereafter for a total of 30 min. In normal individuals and patients with common duodenal ulcer, secretin produces no change, small reductions, or small increases in serum gastrin levels. In contrast, in gastrinoma patients, intravenous secretin induces substantial increases in serum gastrin. The serum gastrin levels increase promptly by at least 200 pg/mL, usually at 5 min (and virtually always by 10 min), and then gradually decrease toward or to preinjection levels by 30 min. In the *calcium infusion test*, serum samples for gastrin measurements are obtained before and at 30-min intervals for 4 h after initiation of a constant 3-h intravenous infusion of calcium gluconate (5 mg calcium per kilogram per hour). In gastrinoma patients, serum gastrin concentrations usually increase above the basal serum gastrin level by more than 400 pg/mL. The third provocative test involves the *feeding of a standard meal*: Gastrin is measured in serum samples obtained before the meal and at 15-min intervals after it for 90 min. This test has been used to attempt to distinguish between patients with gastrinoma and those with hypergastrinemia and gastric acid hypersecretion due to antral gastrin cell hypertrophy or hyperplasia.

The secretin injection test is by far the most valuable provocative test in identifying gastrinoma patients. Positive serum gastrin responses to intravenous secretin are found in more than 95 percent of patients with gastrinoma. Using the criteria suggested, substantial increases in serum gastrin following secretin injection have been detected only rarely in nongastrinoma patients. Reduced gastric acid

secretion, achlorhydria or profound hypochlorhydria, is by far the most common cause of hypergastrinemia. For this reason, gastric acid secretion should be measured before consideration of the secretin injection test. Exaggerated release of gastrin in response to calcium infusion is found in more than 80 percent of gastrinoma patients; however, this exaggerated response to calcium infusion occurs in some nongastrinoma patients with hypergastrinemia (e.g., with achlorhydria). Enhanced gastrin release with calcium infusion is rarely observed in gastrinoma patients in the absence of the abnormally large gastrin release in response to secretin. Since the calcium infusion test does not add significantly to the sensitivity or specificity of the secretin injection test, and since calcium infusion is potentially more hazardous, it is usually not necessary or recommended.

In a very small proportion of duodenal ulcer patients (much less than 1 percent), gastric acid hypersecretion may be accompanied by increased serum gastrin levels due to hyperfunction and/or hyperplasia of antral gastrin cells (G cells). These patients can be distinguished from those with gastrinoma by the secretin injection and meal stimulation tests. In patients with this antral gastrin cell abnormality, intravenous secretin does not produce large increases in serum gastrin characteristic of gastrinoma. Some authors have reported increases in serum gastrin concentrations greater than 200 percent after test meals in patients with gastrin cell hypertrophy or hyperplasia, suggesting that this may be of value distinguishing these patients from those with gastrinoma. Other authors more recently have found similarly large amounts of gastrin released into the sera of patients with gastrinomas, suggesting that the meal-stimulated test is of limited value in distinguishing between patients with antral gastrin cell hyperplasia and those with gastrinoma.

TREATMENT In general, patients with Z-E syndrome are resistant to those medical therapies and surgical procedures designed for and usually effective in treating common peptic ulcer. Antacids may produce transient symptom relief but rarely, if ever, induce ulcer healing or sustained relief of symptoms. Incomplete gastric resection (with or without vagotomy) or pyloroplasty with vagotomy is frequently followed by prompt and often fulminant ulcer recurrence. In the past, many patients with gastrinoma had multiple surgical procedures, particularly in those instances in which the diagnosis was not established initially. Mortality was reported to be lowest in patients with the Z-E syndrome in whom gastrectomy was the initial gastric surgery. This led to the conclusion that when surgery was required in gastrinoma patients, total gastrectomy was the surgical procedure of choice.

Development of effective drugs to reduce acid secretion and more precise diagnostic techniques to locate gastrinomas have increased substantially the therapeutic options. The key to management in these patients is individualization of treatment, since patients with the Z-E syndrome are highly heterogeneous with respect to clinical manifestations and extent of disease. As with many other predominantly malignant tumors, the ideal treatment is removal of the gastrinoma.

H-2 receptor antagonists are effective in reducing gastric acid secretion, producing symptom relief, and inducing ulcer healing in patients with the Z-E syndrome. *Cimetidine* was the first H-2 receptor antagonist used successfully in the treatment of these patients. Improvement in clinical symptoms, decreases in gastric acid output, and ulcer healing were found in 80 to 85 percent. Administration of cimetidine was required at 4- to 6-h intervals, with total daily doses usually four to eight times those used in the treatment of common duodenal ulcer. More recently, *ranitidine*, *famotidine*, and *nizatidine* also have been shown effective in treatment of patients with the Z-E syndrome. These H-2 receptor antagonists require comparable increases in dosage when compared with doses used in treatment of common duodenal ulcer. When instituted, H-2 receptor antagonist therapy must be continued indefinitely, since even temporary discontinuance is usually followed by ulcer recurrence. Ulcers fail to respond or recur while on treatment with H-2 receptor antagonists in approximately 25 percent of patients with the Z-E syndrome. The dose of H-2 receptor antagonist required to maintain a satisfactory reduction in gastric acid secretion can be assessed by measuring the basal gastric acid output during the hour immmediately prior to the next anticipated dose of the drug; the goal is to reduce gastric acid output to less than 10 mmol/h at that time.

Omeprazole, the parietal cell H^+,K^+-ATPase inhibitor, is the most effective drug and agent of choice in reducing gastric acid secretion and in healing ulcer in Z-E patients, including those with ulcers resistant to treatment with H-2 receptor antagonists. As a function of potency and dosage, the effectiveness of omeprazole can be prolonged and sustained. The usual initial daily recommended dose of omeprazole is 60 mg in a single dose administered in the morning before breakfast. The dose is adjusted to maintain gastric acid secretion to less than 10 mmol/h during the hour immediately before the next dose is due. Twice a day dosing is recommended if the patient requires 100 mg or more omeprazole per day. Some Z-E patients, in whom gastrinomas could not be identified or removed surgically, have been treated with parietal cell vagotomy, which has reduced or, in a few instances, eliminated the dose of H-2 receptor antagonist required in these patients.

Treatment for patients with the Z-E syndrome should be individualized. In selecting the best therapy, the biologic behavior of the tumor and the clinical manifestations in each patient must be taken into consideration. Early studies indicated that morbidity and mortality in patients with the Z-E syndrome were due principally to complications of severe ulcer disease. However, with earlier diagnosis, effective antiulcer treatment, and longer follow-up, more frequent consequences of the malignant properties of gastrinoma are now recognized. Approximately 50 percent of patients with the Z-E syndrome in whom the gastrinoma has not been removed will die from malignant invasion by the tumor. Complete *surgical resection of the tumors*, when possible, represents *optimal treatment in patients with gastrinoma*. Complete surgical removal of gastrinoma, with cure, has been achieved in approximately 25 percent of patients with the Z-E syndrome. Successful resection of tumor in Z-E patients with sporadic gastrinoma or with gastrinoma with MEN I requires thorough abdominal exploration and recognition and removal of multiple gastrinomas when found, including those in the wall of the duodenum and other extrapancreatic sites. Gastrinoma in lymph nodes and metastatic to the liver should be removed when safe and possible.

Treatment with omeprazole is indicated in the period during which the diagnosis is being established, while the location and extent of the tumor are being determined, and also as treatment prior to anticipated surgery. At present, omeprazole is certainly indicated for patients who are unsatisfactory candidates for surgery, in those who refuse surgery, and in those in whom surgical removal of the tumor is not possible. Patients with aggressively invasive gastrinoma have been treated with streptozotocin and 5-fluorouracil, in some instances combined with doxorubicin, in attempts to reduce tumor bulk and associated symptoms. Success with chemotherapy is limited, with only an initial response of approximately 40 percent and no complete responses. When metastatic and/or otherwise nonresectable gastrinoma is present, control of the ulcer disease may be achieved in most instances by treatment with omeprazole or, rarely, when required, by total gastric resection. There is no convincing evidence that tumor progression is usually influenced by gastrectomy.

STRESS ULCERS AND EROSIONS

A number of acute ulcerative lesions of the gastrointestinal tract are distinct clinically from chronic peptic ulcer. Among these are the acute upper gastrointestinal erosions and ulcers often observed in patients with shock, massive burns, sepsis, and severe trauma. These are often referred to as *stress erosions* and *ulcers*. These lesions, which are frequently multiple, are most common in the acid-secreting portion of the stomach, but they also may occur in the antrum and duodenum.

These erosions and superficial ulcers are extremely frequent and

GOODMAN & GILMAN'S The PHARMACOLOGICAL BASIS OF THERAPEUTICS

Tenth Edition

McGraw-Hill
MEDICAL PUBLISHING DIVISION

New York Chicago San Francisco Lisbon London Madrid Mexico City
Milan New Delhi San Juan Seoul Singapore Sydney Toronto

McGraw-Hill
A Division of The McGraw-Hill Companies

Goodman and Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 10/e

1234567890 DOWDOW 0987654321

ISBN 0-07-135469-7

This book was set in Times Roman by York Graphic Services, Inc. The editors were Martin J. Wonsiewicz and John M. Morriss; the production supervisor was Philip Galea; and the cover designer was Marsha Cohen/Parallelogram. The index was prepared by Irving Condé Tullar and Coughlin Indexing Services, Inc.
R.R. Donnelley and Sons Company was printer and binder.

This book is printed on acid-free paper.

Library of Congress Cataloging-in-Publication Data

Goodman and Gilman's the pharmacological basis of therapeutics.—10th ed. / [edited by]
Joel G. Hardman, Lee E. Limbird, Alfred Goodman Gilman.
p. ; cm.
Includes bibliographical references and index.
ISBN 0-07-135469-7
1. Pharmacology. 2. Chemotherapy. I. Title: Pharmacological basis of therapeutics.
II. Goodman, Louis Sanford III. Gilman, Alfred IV. Hardman, Joel G.
V. Limbird, Lee E. VI. Gilman, Alfred Goodman
[DNLM: 1. Pharmacology. 2. Drug Therapy. QV 4 G6532 2002]
RM300 G644 2001
615'.7—dc21 2001030728

INTERNATIONAL EDITION ISBN 0-07-112432-2

increase in cytosolic Ca^{2+}. Both pathways activate the H^+,K^+–ATPase (the proton pump). The H^+,K^+–ATPase consists of a large α-subunit and a smaller β-subunit. This pump generates the largest ion gradient known in vertebrates, with an intracellular pH of about 7.3 and an intracanalicular pH of about 0.8.

The most important structures in the central nervous system (CNS) involved in central stimulation of gastric acid secretion are the dorsal motor nucleus of the vagal nerve (DMNV), the hypothalamus, and the nucleus tractus solitarius (NTS). Efferent fibers originating in the DMNV descend to the stomach *via* the vagus nerve and synapse with ganglion cells of the enteric nervous system (ENS). ACh release from postganglionic vagal fibers can stimulate directly gastric acid secretion through a specific muscarinic cholinergic receptor subtype, M_3, located on the basolateral membrane of the parietal cells. The CNS probably modulates the activity of the ENS with ACh as its main regulatory neurotransmitter. The CNS generally is thought of as the main contributor to the initiation of gastric acid secretion in response to the sight, smell, taste, and anticipation of food ("cephalic phase"). ACh also indirectly affects the parietal cell through the stimulation of histamine release from the enterochromaffin-like (ECL) cells in the fundus and the stimulation of gastrin release from the G cells in the gastric antrum.

Histamine is released from ECL cells through multifactorial pathways and is a critical regulator of acid production through the H_2 subtype of receptor. ECL cells usually are found in close proximity to parietal cells. Histamine activates the parietal cell in a paracrine fashion; it diffuses from its release site to the parietal cell. Its involvement in gastric acid secretion (whether or not as the final, common, effector hormone) has been convincingly demonstrated by the inhibition of acid secretion with the use of H_2-receptor antagonists. The ECL cells are the sole source of gastric histamine involved in acid secretion.

Gastrin primarily is present in the antral G cells. As with histamine, the release of gastrin is regulated through multifactorial pathways involving, among other factors, central neural activation, local distention, and chemical components of the gastric content. Gastrin stimulates acid secretion predominantly in an indirect manner by causing the release of histamine from ECL cells; a less-important, direct effect of gastrin on parietal cells also is seen.

Somatostatin, localized in the antral D cells, may inhibit gastrin secretion in a paracrine matter, but its exact role in the inhibition of gastric acid secretion remains to be defined. There appears to be a decrease in D cells in patients with *Helicobacter pylori* infection, and this may lead to excess gastrin production due to a reduced inhibition by somatostatin.

Gastric Defense. The stomach protects itself from damage by gastric acid through several mechanisms such as the presence of intercellular tight junctions between the gastric epithelial cells, the presence of a mucin layer overlying the gastric epithelial cells, the presence of prostaglandins in the gastric mucosa, and secretion of bicarbonate ions into the mucin layer. Prostaglandins E_2 and I_2 inhibit gastric acid secretion by a direct effect on the parietal cell mediated by the EP_3 receptor (*see* section entitled "Prostaglandin Analogs," below). In addition, prostaglandins enhance mucosal blood flow and stimulate secretion of mucus and bicarbonate.

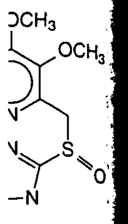
AGENTS USED FOR SUPPRESSION OF GASTRIC ACID PRODUCTION

Figure 37–1 provides the rationale and pharmacological basis for the classes of drugs currently used to combat acid-peptic diseases. The most commonly used agents at present are the proton pump inhibitors and the histamine H_2-receptor antagonists.

Proton Pump Inhibitors

Chemistry, Mechanism of Action, and Pharmacological Properties. The most effective suppressors of gastric acid secretion undoubtedly are the gastric H^+,K^+–ATPase (proton pump) inhibitors. They are the most effective drugs used in antiulcer therapy and have found worldwide popularity over the past decade. Currently, there are several different proton pump inhibitors available for clinical use: *omeprazole* (PRILOSEC), *lansoprazole* (PREVACID), *rabeprazole* (ACIPHEX), and *pantoprazole* (PROTONIX). They are α-pyridylmethylsulfinyl benzimidazoles with different substitutions on the pyridine or the benzimidazole groups; their pharmacological properties are similar. Proton pump inhibitors are "prodrugs," requiring activation in an acid environment. These agents enter the parietal cells from the blood and, because of their weak basic nature, accumulate in the acidic secretory canaliculi of the parietal cell, where they are activated by a proton-catalyzed process that results in the formation of a thiophilic sulfenamide or sulfenic acid (Figure 37–2). This activated form reacts by covalent binding with the sulfhydryl group of cysteines from the extracellular domain of the H^+,K^+–ATPase. Binding to cysteine 813, in particular, is essential for inhibition of acid production, which is irreversible for that pump molecule. Proton pump inhibitors have profound effects on acid production. When given in a sufficient dose (*e.g.*, 20 mg of omeprazole a day for seven days), the daily production of acid can be diminished by more than 95%. Secretion of acid resumes only after new molecules of the pump are inserted into the luminal membrane. Omeprazole also selectively inhibits gastric mucosal carbonic anhydrase, which may contribute to its acid suppressive properties.

Pharmacokinetics. Proton pump inhibitors are unstable at a low pH. The oral dosage forms ("delayed release") are supplied as enteric-coated granules encapsulated in a gelatin shell (omeprazole and lansoprazole) or as enteric-coated tablets (pantoprazole and rabeprazole). The granules dissolve only at an alkaline pH, thus preventing degradation of the drugs by acid in the esophagus and stomach. Proton pump inhibitors are rapidly



PRAZOLE

contraindications to oral ingestion, but this picture is expected to change with the advent of intravenous preparations of proton pump inhibitors. *Pantoprazole,* a relatively more acid-stable compound, is the first such preparation to be approved in the United States. A single intravenous bolus of 80 mg can inhibit acid production by 80% to 90% within an hour, an effect that can last up to 21 hours. Therefore, once-daily dosing of intravenous proton pump inhibitors (in doses similar to those used orally) may be sufficient to achieve the desired degree of hypochlorhydria. The clinical utility of these formulations in the above situations will require further study but is expected to be equal to if not greater than that of intravenous H_2-receptor antagonists.

The requirement for acid to activate these drugs within the parietal cells has several important consequences. The drugs should be taken with or before a meal, since food will stimulate acid production by parietal cells; conversely, coadministration of other acid-suppressing agents such as H_2-receptor antagonists may diminish the efficacy of proton pump inhibitors. Since not all pumps or all parietal cells are functional at the same time, it takes several doses of the drugs to result in maximal suppression of acid secretion. With once-a-day dosing, steady-state inhibition, affecting about 70% of pumps, may take 2 to 5 days (*see* Sachs, 2000). Achieving steady-state inhibition may be accelerated somewhat by more frequent dosing initially (*e.g.,* twice daily). Since the binding of the drugs' active metabolites to the pump is irreversible, inhibition of acid production will last for 24 to 48 hours or more, until new enzyme is synthesized. The duration of action of these drugs, therefore, is not directly related to their plasma half-lives.

Adverse Effects and Drug Interactions. Proton pump inhibitors inhibit the activity of some hepatic cytochrome P450 enzymes and therefore may decrease the clearance of benzodiazepines, warfarin, phenytoin, and many other drugs. When disulfiram is coadministered with a protein pump inhibitor, toxicity has been reported. Proton pump inhibitors usually cause few adverse effects; nausea, abdominal pain, constipation, flatulence, and diarrhea are the most common side effects. Subacute myopathy, arthralgias, headaches, and skin rashes also have been reported.

Chronic treatment with omeprazole decreases the absorption of vitamin B_{12}, but insufficient data exist to demonstrate whether or not this leads to a clinically relevant deficiency. Hypergastrinemia (>500 ng/liter) occurs in approximately 5% to 10% of long-term omeprazole users. Gastrin is a trophic factor for epithelial cells, and there is a theoretical concern that elevations in gastrin can promote the growth of different kinds of tumors in the gastrointestinal tract. In rats undergoing long-term administration of proton pump inhibitors, there has been development of enterochromaffin-like cell hyperplasia and gastric carcinoid tumors secondary to sustained hypergastrinemia; this has raised concerns about the possibility of similar complications in human beings. There are conflicting data on the risk and clinical implications of enterochromaffin-like cell hyperplasia in patients on long-term proton pump inhibitor therapy. These drugs now have a track record of more than 15 years of use worldwide, and no major new issues regarding safety have emerged (Klinkenberg-Knol *et al.,* 1994; Kuipers and Meuwissen, 2000). There is as yet no reason to believe, therefore, that hypergastrinemia should be a trigger for discontinuation of therapy or that gastrin levels should be monitored routinely in patients on long-term proton pump inhibitor therapy. However, the development of a hypergastrinemic state may predispose the patient to rebound hypersecretion of gastric acid following discontinuation of therapy.

Proton pump inhibitors have not been associated with a major teratogenic risk when used during the first trimester of pregnancy; caution, however, is still warranted.

Therapeutic Uses. Proton pump inhibitors are used principally to promote healing of gastric and duodenal ulcers and to treat *g*astric *e*sophageal *r*eflux *d*isease (GERD) that is either complicated or unresponsive to treatment with H_2-receptor antagonists (*see* below). Proton pump inhibitors also are the mainstay in the treatment of Zollinger-Ellison syndrome. Therapeutic applications of proton pump inhibitors are further discussed later in this chapter, under "Specific Acid-Peptic Disorders and Therapeutic Strategies."

HISTAMINE H_2-RECEPTOR ANTAGONISTS

The description of selective histamine H_2-receptor blockade by Black in 1970 was a landmark in the history of pharmacology and set the stage for the modern approach to the treatment of acid-peptic disease, which until then had relied almost entirely on acid neutralization in the lumen of the stomach (*see* Black, 1993; Feldman and Burton, 1990a,b). Equally impressive has been the safety record of H_2-receptor antagonists, a feature that eventually led to their availability without a prescription. Increasingly, however, these agents are being replaced by the more efficacious albeit more expensive proton pump inhibitors.

Chemistry, Mechanism of Action, and Pharmacological Properties. Four different H_2-receptor antagonists are currently on the market in the United States: *cimetidine* (TAGAMET), *ranitidine* (ZANTAC), *famotidine* (PEPCID), and *nizatidine* (AXID) (Figure 37–3). Their different chemical structures do not alter the drugs' clinical efficacies as much as they determine interactions with other drugs and change the side-effect profiles. H_2-receptor antagonists inhibit acid production by reversibly competing with histamine for binding to H_2 receptors on the basolateral membrane of parietal cells.

The most prominent effects of H_2-receptor antagonists are on basal acid secretion; less profound but still significant is suppression of stimulated (feeding, gastrin, hypoglycemia, or vagal stimulation) acid production. These agents thus are particularly effective in suppressing

Severity of GERD		Medical Management*
Stage I Sporadic uncomplicated heartburn, often in setting of known precipitating factor. Often not the chief complaint. Less than 2-3 episodes per week. No additional symptoms.	→	Lifestyle modification, including diet, positional changes, weight loss, *etc.* Antacids and or Histamine H_2-receptor antagonists as needed
Stage II Frequent symptoms, with or without esophagitis. Greater than 2-3 episodes per week.	→	Proton pump inhibitors more effective than Histamine H_2-receptor antagonists
Stage III Chronic, unrelenting symptoms; immediate relapse off therapy. Esophageal complications (*e.g.*, stricture, Barrett's metaplasia)	→	Proton pump inhibitor either once or twice daily

Figure 37–6. General guidelines for medical management of gastroesophageal reflux disease (GERD).

*Only acid production–suppressing and acid-neutralizing medication included. *(Adapted from Wolfe and Sachs, 2000, with permission.)*

decades; so has the incidence of esophageal adenocarcinoma, particularly in white males. An association has been suggested between GERD symptoms and the incidence of esophageal adenocarcinoma (Lagergren *et al.*, 1999). An increasing number of reports also link GERD and tracheopulmonary symptoms such as chronic laryngitis and asthma, although a cause-and-effect relationship is still somewhat controversial. Finally, it should be borne in mind that GERD is a chronic disorder that requires long-term therapy (DeVault, 1999).

Although the pathophysiology of GERD has more to do with a disturbance of gastrointestinal motility (*see* Chapter 38), most of the symptoms are due to the injurious effects of the acid-peptic refluxate on the esophageal epithelium. This provides the rationale for the current pharmacotherapeutic approach to treating this syndrome, which is based on suppression of gastric acid. Traditional prokinetic agents have been of limited efficacy, but more specific agents currently are being developed and may hold greater promise (Chapter 38).

Treatment of Acute GERD Symptoms. The goals of GERD therapy are complete resolution of symptoms and healing of esophagitis. Proton pump inhibitors are clearly more effective than H_2-receptor antagonists in achieving both of these goals. Healing rates after 4 weeks and 8 weeks of therapy with proton pump inhibitors are around 80% and 90%, respectively; healing rates with H_2-receptor antagonists are 50% and 75%. Indeed, proton pump inhibitors are so effective that their empirical use has been advocated as a therapeutic trial in patients in whom GERD is suspected to play a role in the pathogenesis of symptoms. The "omeprazole test" involves giving omeprazole for a period of 12 weeks to patients with noncardiac chest pain. Expensive diagnostic tests are instituted only if such a trial fails (Fass *et al.*, 1998). Because of the wide clinical spectrum associated with GERD, the therapeutic approach is best tailored to the level of severity in the individual patient (Figure 37–6). In general, the optimal dose for each individual patient should be determined based upon symptom control. Only in patients with complicated GERD and/or Barrett's esophagus is documentation of complete acid control with 24-hour pH monitoring indicated.

Regimens for the treatment of GERD with proton pump inhibitors and histamine H_2-receptor antagonists are listed in Table 37–4. Although some patients with mild GERD symptoms may be managed by nocturnal doses of H_2-receptor antagonists, dosing two or more times a day generally is required. In patients with severe symptoms or extraintestinal manifestations of GERD, twice-daily dosing with a proton pump inhibitor may be needed. It has been shown, though, that nocturnal acid breakthrough can occur even with twice-daily proton pump inhibitor dosing in healthy subjects and that this can be controlled by the addition of an H_2-receptor antagonist at bedtime (Peghini *et al.*, 1998). The clinical importance of this finding for GERD patients with poorly responsive symptoms to standard dosing of proton pump inhibitors needs further evaluation.

A popular approach to GERD therapy, encouraged by managed-care companies, consists of a "step-up" regimen, beginning with an H_2-receptor antagonist and only progressing to one of the proton pump inhibitors if symptoms fail to respond. While theoretically appealing, this approach carries the risk of